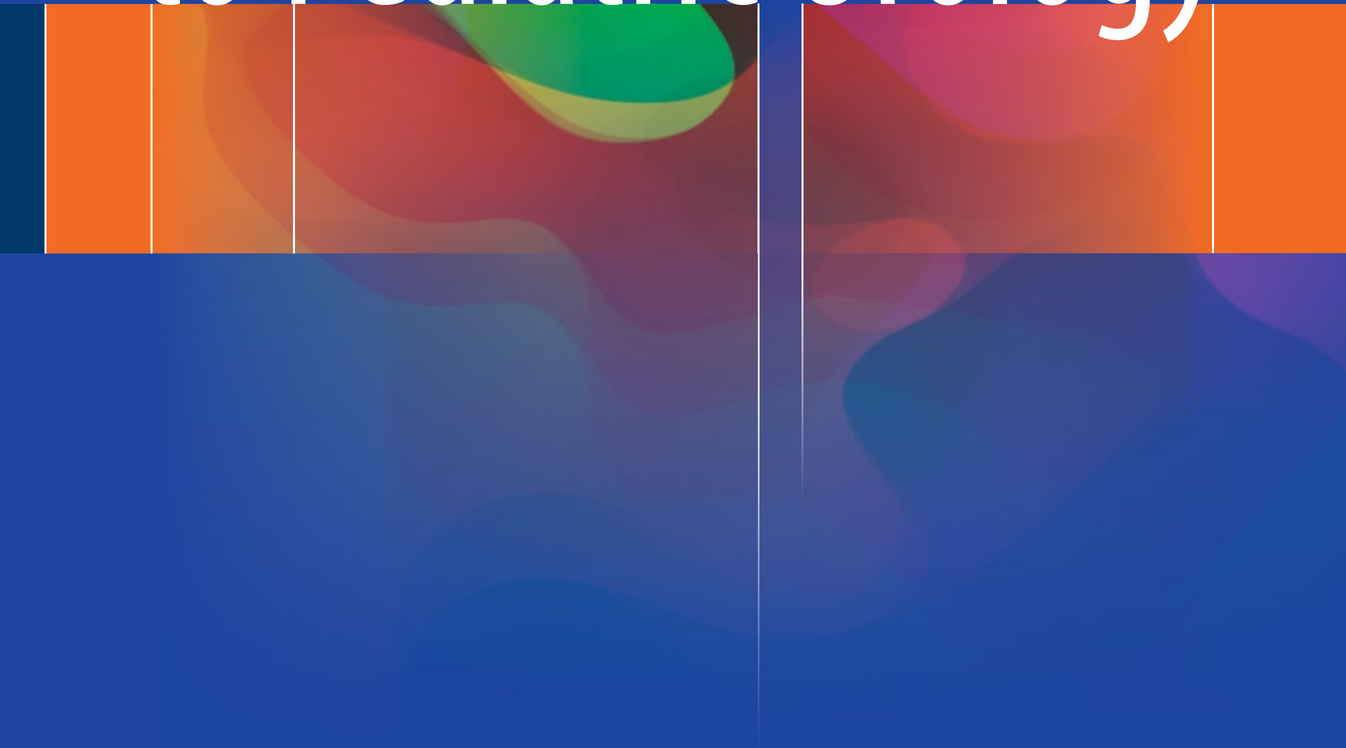
Ahmed H. Al-Salem

An Illustrated Guide to Pediatric Urology



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Ahmed H. Al-Salem

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ISBN 978-3-319-44181-8 ISBN 978-3-319-44182-5 (eBook)
DOI 10.1007/978-3-319-44182-5

Library of Congress Control Number: 2016957149

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Printed on acid-free paper

Springer Cham Heidelberg New York Dordrecht London
This Springer imprint is published by Springer Nature

Preface

The field of pediatric urology is rapidly growing and currently it is considered as a subspecialty. Pediatric urologists and pediatric surgeons care for newborns, infants, and children with congenital and acquired urological conditions. I have written this book with more than 20 years' experience in the care of infants and children with urological conditions and hope it will help all those involved in the surgical care of infants and children with urological problems. This book is written in a simple way and easy to read. It covers most areas in the field of pediatric urology with emphasis on the most important points relevant to the patient's presentation, diagnosis, and management. This book is well illustrated and includes clinical, operative, radiological, and hand-drawn illustrations. I hope it will be useful to consultant pediatric urologists, pediatric surgeons, specialists, fellows, and residents. This book should be useful also to general practitioners, general surgeons, accident and emergency doctors, pediatricians, neonatologists, trainees, medical students, and nurses.

Qatif, Saudi Arabia
Ahmed H. Al-Salem

Acknowledgments

I would like to express special thanks of gratitude to my family who supported me and made this project possible. I would also like to thank all my patients and their families.

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Congenital Urological Malformations

1

1.1 Introduction

- The urinary system is comprised of two kidneys, two ureters, a bladder and a urethra.
- The kidneys contains the nephrons which are responsible to filter the blood as it passes through the kidney.
- It is estimated that the kidneys will filter around 190 l of water every day from the blood. Most of the water from the blood that is filtered is reabsorbed into the body and the remaining water is excreted as urine.
- This water travels down the ureters to the bladder which acts as a storage area for the urine.
- When the bladder reaches a certain volume, nerves in the walls of the bladder are stimulated and urination happens.
- The kidneys also play an important role in red blood cell production. Erythropoietin, which is produced in the kidneys stimulates the production of the red blood cells.
- Congenital anomalies of the kidney and urinary tract (CAKUT) are common in children.
- They represent approximately 30 % of all prenatally diagnosed malformations.
- Congenital anomalies of the kidney and urinary tract occur in 3–6 per 1,000 live births.
- They account for the most cases of pediatric end-stage kidney disease (ESKD), and predispose an individual to hypertension and cardiovascular disease throughout life.
- They are responsible for 34–59 % of chronic kidney disease (CKD) and for 31 % of all cases of end-stage kidney disease (ESKD) in children.
- Congenital anomalies of the kidney and urinary tract comprise a wide range of structural and functional malformations that occur at the level of:
  - The kidney
  - Collecting system
  - Bladder
  - Urethra
- With improved prenatal screening, many cases of CAKUT are diagnosed by antenatal ultrasonography performed on 18–20 weeks of gestation.
- Most common antenatal manifestations of CAKUT include oligohydramnios or variations in gross morphology of the kidney, ureter, or bladder.
- CAKUTs anomalies can be:
  - Sporadic
  - Familial
  - Syndromic
  - Nonsyndromic
- Syndromic CAKUTs:
  - They develop in association with other additional congenital abnormalities outside of the kidney and urinary tract.
  - They manifest clinically recognizable features of a known syndrome.

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A.H. Al-Salem, *An Illustrated Guide to Pediatric Urology*, DOI 10.1007/978-3-319-44182-5_1

- Nonsyndromic CAKUT:
  - Congenital structural anomalies confined only to the kidney and urinary tract.
- Genetic causes have been identified in association with the syndromic forms of congenital malformations.
- The spectrum of congenital anomalies includes more common anomalies such as vesicoureteral reflux and, rarely, more severe malformations such as bilateral renal agenesis.
- These congenital anomalies can be unilateral or bilateral, and sometimes different defects coexist in the same child.
- It is important to recognize and diagnose these anomalies early as early treatment will minimize renal damage, prevent or delay the onset of ESRD, and provide supportive care to avoid complications of ESRD.

1.2 Normal Embryology

- The two most common congenital bladder abnormalities are:
  - Bladder exstrophy
  - Congenital diverticula
- An exstrophic bladder is one that is open to the outside and turned inside out, so that its inside is visible at birth, protruding from the lower abdomen.
- A diverticulum is an extension of a hollow organ, usually shaped like a pouch with a narrow opening.
- The terminal portion of the hindgut is called the cloaca.
- The cloaca forms the future urinary and gastrointestinal tracts.
- The cloaca is formed early in fetal life by incorporation of the allantois to form a common distal channel for the primitive urinary and gastrointestinal systems.
- The most caudal portion of the cloaca is the cloacal membrane.
- This separates the cloaca from the amniotic cavity.
- During the fourth to seventh weeks of development, the cloaca is divided by the urorectal septum into anterior and posterior portions to form the urogenital sinus and anal canal, respectively.
- The urogenital sinus further differentiates into three anatomic components:
  - The vesical (cranial) portion
  - The pelvic (middle) portion
  - The phallic (caudal) portion
- The pelvic and phallic portions will form the urethra and genitals, respectively.
- The vesical portion forms most of the bladder and is continuous with the allantois.
- The allantois normally constricts to a thick fibrous cord, the median umbilical ligament, and extends from the apex of the bladder to the umbilicus.
- The trigone portion of the bladder is formed from the caudal ends of the mesonephric ducts, which are incorporated into the developing bladder wall.
- The ureters are formed from the ureteral buds.
- The ureteral bud is an outgrowth of the mesonephric duct near its entrance into the cloaca. This will elongate and develop into the ureter.
- The more distal ureteral bud undergoes a complex interaction with the primitive kidney to induce differentiation of the renal parenchyma and formation of the renal pelvis, calyces, and collecting tubules.
- As the kidneys develop and ascend, traction on the ureters causes the ureteral orifices to move superolaterally, resulting in an oblique course through the muscular wall at the base of the bladder.
- The kidneys are paired organs located retroperitoneally. Their vascular supply comes from the renal arteries, and they drain into the renal veins. Each kidney excretes into a ureter, which will in turn empty into the urinary bladder. Its functional unit is the nephron.
- The urogenital system arises from intermediate mesoderm which forms a urogenital ridge on either side of the aorta.
- The urogenital ridge develops into three sets of tubular nephric structures (from head to tail): the pronephros, the mesonephros, and the metanephros.
- During the development of the kidney, there are three main structures initially, which

derive from intermediate mesoderm. These structures are pronephros, mesonephros and metanephros.

- The development of the kidney proceeds through a series of three successive phases, each marked by the development of a more advanced kidney:
  - The pronephros
  - The mesonephros
  - The metanephros
- The pronephros:
  - This is the most immature form of the kidney.
  - During approximately day 22 (fourth embryonic week) of human gestation, the paired pronephros appear towards the cranial end of the intermediate mesoderm.
  - It develop as a condensation of intermediate mesoderm in the lower cervical and upper thoracic regions extending to the cloaca, and almost entirely regresses in gestational week 4.
  - It appears as seven to ten cell groups and arrange themselves in a series of tubules called nephrotomes and join laterally with the pronephric duct.
  - The pronephric duct, which arises from dorsal and caudal evaginations of the pronephros, is preserved and ultimately will give rise to the mesonephric duct.
- The mesonephros:
  - The mesonephros begins to develop as the pronephros is regressing (fourth week).
  - The development of the pronephric duct proceeds in a cranial-to-caudal direction.
  - As it elongates caudally, the pronephric duct induces nearby intermediate mesoderm in the thoracolumbar area to become epithelial tubules called mesonephric tubules.
  - It starts as a series of S-shaped tubules.
  - Each mesonephric tubule receives a blood supply from a branch of the aorta, ending in a capillary tuft analogous to the glomerulus of the definitive nephron.
  - The tubules around the glomerulus will form a Bowmann's capsule around the capillary tuft.
  - Together this will lead to the formation of a renal corpuscle allowing for filtration of blood.
  - Laterally, the tubule enters the mesonephric collecting duct (wolffian duct).
  - This filtrate flows through the mesonephric tubule and is drained into the continuation of the pronephric duct, now called the mesonephric duct or Wolffian duct.
  - The nephrotomes of the pronephros degenerate while the mesonephric duct extends towards the most caudal end of the embryo, ultimately attaching to the cloaca.
  - These mesonephric tubules carry out some kidney function at first, but then many of the tubules regress. However, the mesonephric duct persists and opens to the cloaca at the tail of the embryo.
  - In both sexes, the ureters, renal pelvis, and bladder trigone are derived from the mesonephric duct.
  - In males, the mesonephric duct also gives rise to the vasa deferentia, epididymides, and seminal vesicles; the former is part of the duct itself, while the latter two structures arise as a result of ductal dilatation or outpouching.
  - Once the mesonephric duct comes in contact with the cloaca at the caudal aspect of the embryo, it then grows cranially as the ureteric bud until it comes in contact with the metanephric mesenchyme, forming the metanephros.
  - The ureteric bud and metanephric mesenchyme reciprocally induce growth, forming the kidney.
- The metanephros:
  - This gives rise to the definitive kidney.
  - The metanephros develops from several components:
    - An outgrowth of the caudal mesonephric duct
    - The ureteric bud
    - A condensation of nearby renogenic intermediate mesoderm, the metanephric blastema
  - The metanephros appears during the fifth week of intrauterine life.

  - The kidney has two parts:
    - The collecting system
    - The excretory system
  - The collecting system develops from the ureteric bud which is an outgrowth of the mesonephric duct.
    - The ureteric bud penetrates the metanephric tissue.
    - The bud then dilates, forming a renal pelvis.
    - The renal pelvis will differentiate into the major calyces.
    - The major calyces will further differentiate and subdivide for 12 or more generations to form the minor calyces.
    - By the fifth generation, the renal pyramids are formed.
  - The excretory system is formed because a metanephric tissue cap is induced by the collecting tubules to form renal vesicles.
  - The vesicles form an s-shaped tubules which is covered in capillaries, giving rise to glomeruli.
  - The tubules and the glomeruli form the nephron.
  - Continues expansion of the tubules will form the convoluted tubules of the kidney and the loop of Henle.
  - At birth, approximately 750,000–1 million nephrons are present in each kidney; postnatally, renal size may increase, owing to elongation of the proximal convoluted tubules.
  - With differential longitudinal growth of the embryo, the kidney ascends from its initial location in the pelvis to its final location in the upper retroperitoneum.
  - During ascent, transient blood vessels serially arise and degenerate; these arteries persist in ectopic kidneys as well as in some orthotopic renal units.
  - Concurrently, the kidneys rotate around their vertical and horizontal axes so that their final orientation is one in which the upper poles are slightly more medial and anterior than the lower poles.
- The urogenital sinus can be further subdivided into cranial (future bladder) and caudal (future prostate, urethra, and external genitalia) portions.
- The vesical epithelium is entirely derived from the endodermal layer of the urogenital sinus.
- The mesonephric duct gives rise to the ureter.
- With continued caudal growth of the embryo, the proximal end of the mesonephric duct is progressively absorbed caudally and the common portion of the mesonephric duct is absorbed into the bladder trigone and urogenital sinus.
- The discrete branches of the mesonephric duct which will become the male genital ducts and ureters becomes distinct entities attached to the urogenital sinus.
- The nonepithelial layers of the detrusor (non-trigone) portion of the bladder arise from condensations of splanchnic mesenchyme.
- The lumen of the allantois, which connects the bladder and the anterior abdominal wall, closes over time, yielding the urachus. Over time, the urachus becomes more fibrotic and becomes the median umbilical ligament.
- The prostate gland develops around 9–11 gestational weeks from the urogenital sinus, as endoderm invaginates into surrounding mesenchyme.
- Prostate development is an androgen-dependent process.
- It appears that the mesenchyme, rather than the endoderm, must be androgen-sensitive in order for normal prostatic development to occur.
- The urethra develops from the urogenital sinus, with endoderm giving rise to the epithelium and splanchnic mesenchyme giving rise to the surrounding soft tissue.
- In males, the most distal part of the urethra (the glanular portion) appears to arise from an ectodermal invagination which then joins with the endodermal epithelium of the proximal urethra to create a continuous channel.

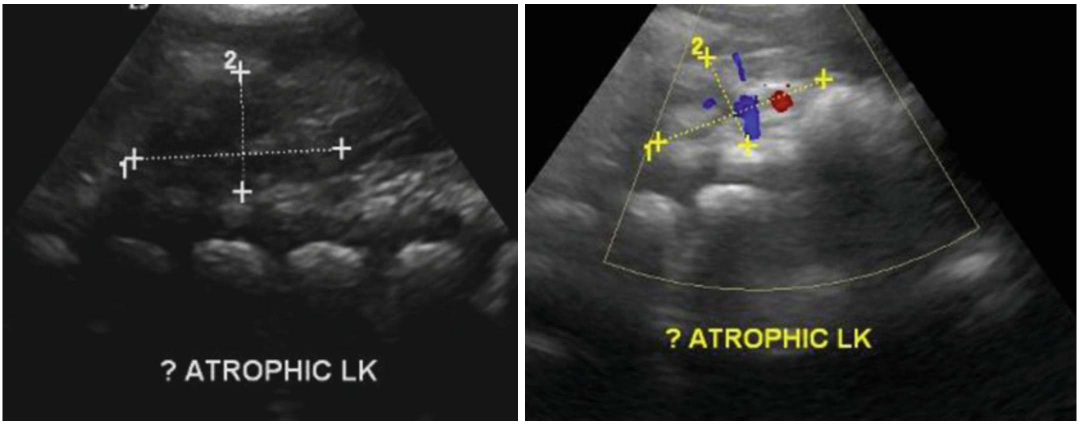
1.3 Abnormalities of the Kidney

- Normal renal development depends upon the interaction between the ureteric bud and metanephric mesenchyme, which induces organogenesis resulting in the formation of the 600,000–2 million nephrons and the collecting system of each kidney.

- The kidney is the most common site of congenital abnormalities.
- Renal malformations are often associated with other congenital defects such as a grossly deformed pinna with ipsilateral abnormalities of the facial bones.

1.3.1 Renal Agenesis

- Renal agenesis is a congenital malformation in which one (unilateral) or both (bilateral) fetal kidneys fail to develop.
- Renal agenesis can be unilateral or bilateral but almost always unilateral.
- Unilateral renal agenesis is a relatively common congenital urinary malformation.
- It is usually diagnosed during fetal ultrasonography or incidentally on ultrasound done for other reasons.
- Some cases of unilateral renal agenesis may represent involution of a previous multicystic disease of the kidney (Figs. 1.1, 1.2, and 1.3).
- Up to 40 % of women with a urogenital tract anomaly also have an associated renal tract anomaly.
- Adults with unilateral renal agenesis have considerably higher chances of hypertension.
- The annual incidence of unilateral renal agenesis is estimated at around 1 in 2,000 live newborns.
- The male to female ratio is around 1.2:1.
- Approximately 56 % of unilateral renal agenesis occurs on the left side.
- Most patients with unilateral renal agenesis are asymptomatic if the other kidney is fully functional.
- However, hypertension, proteinuria and renal failure may develop in the long term follow-ups (20–50 % of cases at the age of 30), which may be based on glomerular hyperfiltration.
- Due to this increased risk of hypertension and/or proteinuria, long-term follow-up of these patients is important.
- Associated malformations:
  - Unilateral renal agenesis may be an isolated congenital malformation or may be associated with chromosomal abnormalities or a variety of nonchromosomal syndromes including the VACTERL and MURCS associations.
  - Congenital cardiac malformations are the most common malformations associated with unilateral renal agenesis.
  - Girls with unilateral renal agenesis should have a pelvic ultrasound to look for abnormalities in the müllerian structures.
  - Vesicoureteral reflux is the most common abnormality noted in the contralateral kidney.
  - It is associated with an increased incidence of Müllerian duct abnormalities, and can



Figs. 1.1 and 1.2 Abdominal ultrasound showing left atrophic kidney. This is most likely following involution of a previous multicystic kidney

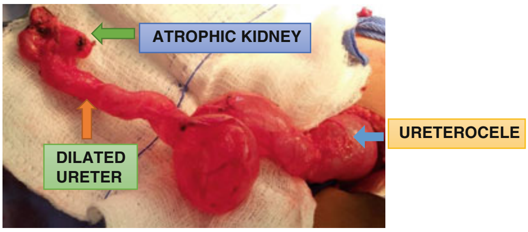


Fig. 1.3 Intraoperative photograph showing a very small atrophic kidney. Note also the massively dilated ureter secondary to an obstructive ureterocele

be a cause of infertility, hematocolpos, increased need for Caesarean sections, or other problems.
- Herlyn-Werner-Wunderlich syndrome is one such syndrome in which unilateral renal agenesis is combined with a blind hemivagina and uterus didelphys.
- Renal agenesis is occasionally associated with genital tract anomalies on the same side such as seminal vesicle hypoplasia and absence of the vas deferens.
- Other anomalies occur in up to 40 % of patients, mainly cardiac (such as atrial or ventricular septal defects) and gastrointestinal (such as anorectal agenesis).

- Renal agenesis results from a development failure of the ureteric bud and the metanephric mesenchyme.
- Unilateral renal agenesis can be caused by mutations in many genes, such as *RET* (10q11.2), *BMP4* (14q22-23), FRAS1 (4q21.21), FREM1 (9p22.3 or UPK3A (22q13.31), PAX2 (10q24.31), HNF1B (17q12), DSTYK (1q32).
- Unilateral renal agenesis can occur as part of multi-organ syndromes, several of which have defined genetic bases, including Kallmann syndrome, branchio-oto-renal syndrome, diGeorge syndrome, Fraser syndrome, MURCS association, Poland syndrome, renal cysts and diabetes syndrome, and Williams-Beuren syndrome.
- Maternal diabetes mellitus or use of specific drugs during pregnancy can also result in renal agenesis.
- Prenatal suspicion of unilateral renal agenesis is confirmed by postnatal ultrasound showing an empty renal fossa, followed by renography to confirm the presence of a solitary functioning kidney.
- The size of the solitary functioning kidney is increased in the majority of patients.
- A voiding cystourethrogram should be considered in order to detect vesicoureteral reflux (VUR).
- The differential diagnoses include:
  - Extreme unilateral renal dysplasia
  - Involuted multicystic dysplastic kidney
  - Renal ectopia
- In most familial cases, unilateral renal agenesis is inherited in an autosomal dominant manner with incomplete penetrance.
- Unilateral renal agenesis can occur with dysplasia or hypoplasia of the solitary functioning kidney which makes the prognosis more serious.

1.3.2 Renal Hypoplasia

- Renal hypoplasia is a common congenital malformations.
- It is poorly understood and commonly used to describe a congenitally small kidneys with a reduced number of nephrons but normal architecture.
- There are however two distinct conditions:
  - Oligomeganephronia:
    - This is a type of renal hypoplasia that results from a quantitative defect of the renal parenchyma with a reduced number of nephrons.
  - Simple renal hypoplasia:
    - This is characterized by reduction in the renal mass but the number of nephrons is normal.
- It was estimated that renal hypoplasia affect about 2.2 % of the population.
- The exact incidence of renal hypoplasia is not known but it is estimated to occur 1 in 400 live births.
- This however is not a true incidence of pure renal hypoplasia because the majority of congenitally small kidneys also exhibit evidence of renal dysplasia.

- Severe bilateral reductions in nephron numbers that are characteristic of renal hypoplasia/dysplasia are the leading cause of childhood end stage renal disease.
- A much less reduction in nephron number caused by mild bilateral renal hypoplasia, have been associated with the development of adult-onset hypertension and chronic renal failure.
- The diagnosis of hypertension in patients with unilateral hypoplasia/dysplasia is an indication for nephrectomy.
- Oligomeganephronia:
  – This results from arrested development of the metanephric blastema at 14–20 weeks' gestation, with subsequent hypertrophy of glomeruli and tubules in the kidney.
  – This hypertrophy and hyperfiltration results in further nephron injury and sclerosis. Eventually, this progressive loss of nephrons leads to end-stage renal disease (ESRD).
  – Oligomeganephronia is usually found in infants in their first year of life and presents with anorexia, vomiting, and failure to thrive.
  – After the first year of life, individuals with oligomeganephronia most often present with short stature, polyuria and polydipsia, or proteinuria.

1.3.3 Supernumerary Kidneys

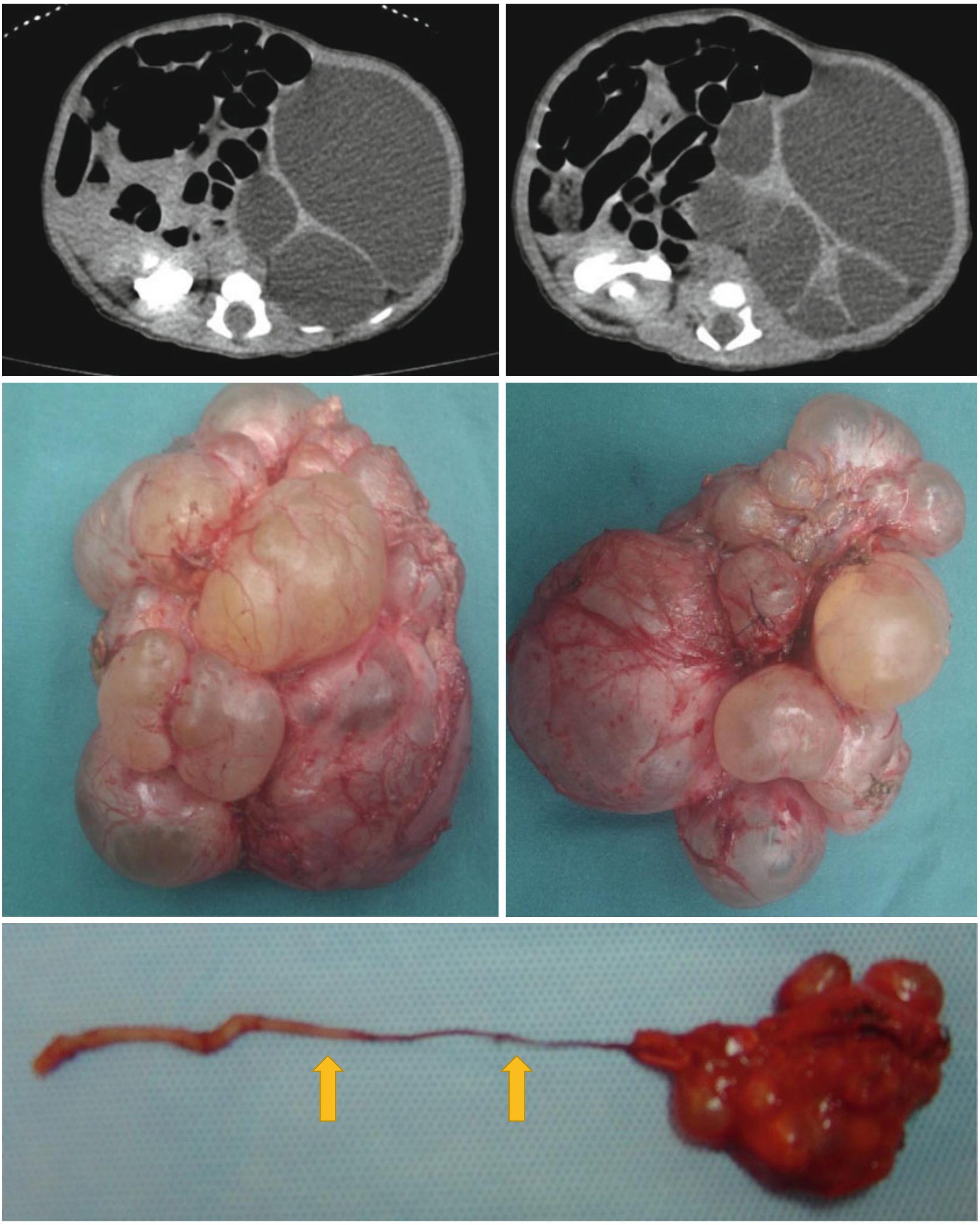
- Supernumerary kidneys are a rare congenital anomaly of the urogenital system, where there are one or two accessory kidneys.
- A third kidney may be confused with the relatively common unilateral duplication of the renal pelvis.
- Supernumerary kidney results from the aberrant division and splitting of the nephrogenic blastema into two metanephric blastemas or from separate metanephric blastemas into which partially or completely reduplicated ureteral stalks enter to form separate capsulated kidneys.
- The end result is two kidneys in association with a partially or completely duplicated ureteral bud.
- In some cases the separation of the reduplicated organ is incomplete forming fused supernumerary kidney.
- Associated anomalies:
  – Urogenital anomalies such as fusion anomalies, ectopic ureteric opening, vaginal and uretral atresia, urethral or penile duplication.
  – Non-urogenital anomalies such as coarctation of aorta, imperforate anus, ventricular septal defect and meningomyelocele.
- Supernumerary kidneys are most commonly located on the left side of the abdomen.
- A supernumerary kidney may be of same size as, larger than, or more commonly smaller than the usual kidney.
- It functions normally, possess a normal shape and capsule, and is either not attached to or loosely attached to the normal kidney but in an abnormal location.
- A supernumerary kidney may be located in front, below, above, or behind the normal kidney. They can also be found in the iliac region or anterior to the sacral promontory.
- The supernumerary kidney is thought to be an accessory organ with a separate arterial supply, venous drainage, collecting system, and distinct encapsulated tissue.
- It may have either a separate ureter or more commonly bifid ureters (50 %). Rarely the ureter of the supernumerary kidney may have an ectopic opening.
- Symptoms have been noted in approximately two-thirds of the reported cases of supernumerary kidney. When symptomatic they may cause fever, pain, or palpable abdominal mass.
- The diagnosis of supernumerary kidney can be made by:
  – IVU
  – Ultrasonography
  – Nuclear scintigraphy
  – CT
  – MRI
- Bilateral supernumerary kidney is extremely rare.
- Surgery is indicated when supernumerary kidneys are affected by pathologic conditions and become symptomatic

1.3.4 Renal Dysplasia and Multicystic Kidney (Figs. 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 1.10, 1.11, and 1.12)

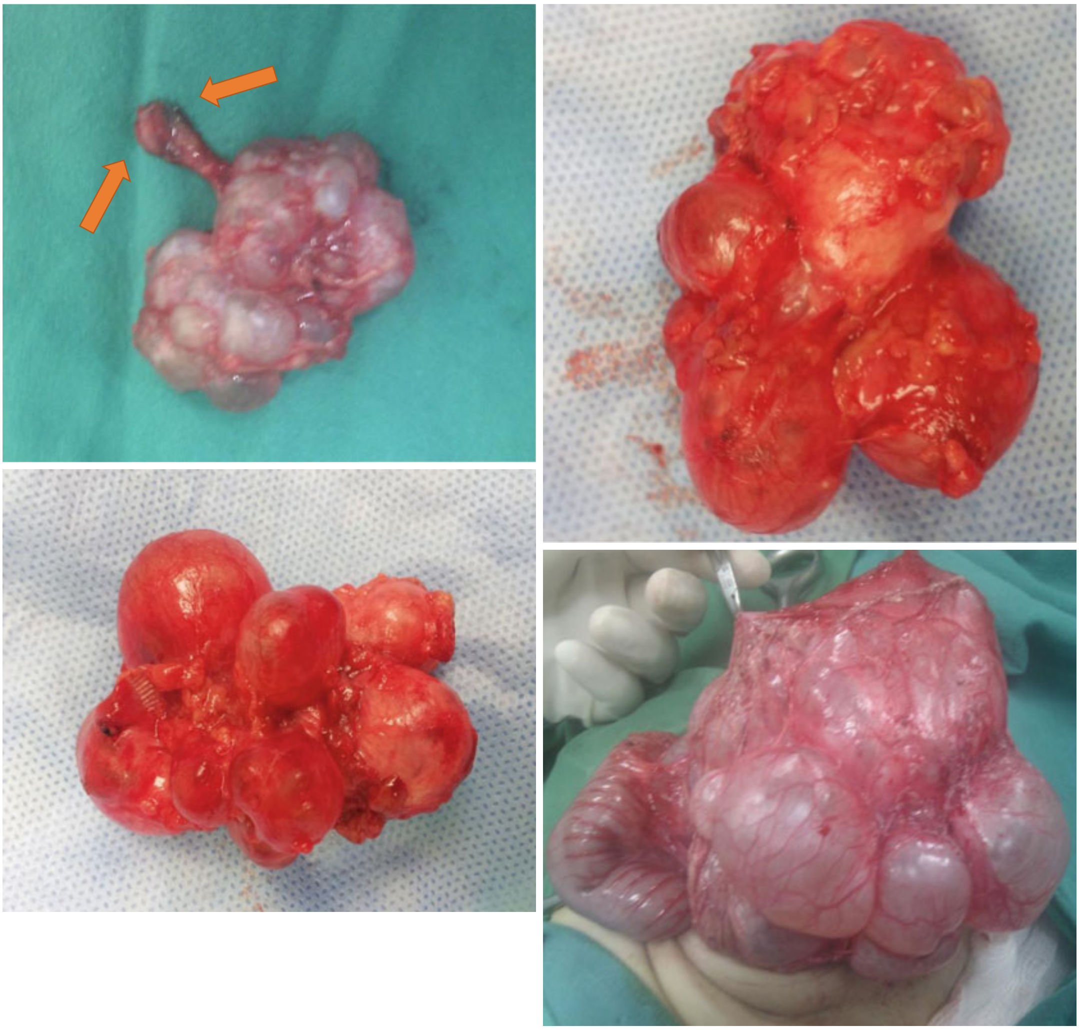
- Renal dysplasia is characterized by the presence of malformed renal tissue elements, including primitive tubules, interstitial fibrosis, and/or the presence of cartilage in the renal parenchyma.
- Multicystic dysplastic kidney (MCDK), a variant of renal dysplasia, is one of the most frequently identified congenital anomalies of the urinary tract.
- Other terms used to describe this condition include multicystic kidney and multicystic renal dysplasia.
- Multicystic kidney of the newborn is normally seen in only one kidney as an irregularly lobulated mass of cysts and usually absent or atretic ureter.
- Multicystic dysplastic kidney is the most common cause of an abdominal mass in the newborn and is the most common cystic malformation of the kidney in infancy.
- Renal dysplasia is considered the leading cause of end-stage renal disease in children.
- Multicystic dysplastic kidney is characterized by:
  - The presence of multiple, noncommunicating cysts of varying size separated by dysplastic parenchyma and the absence of a normal pelvocaliceal system.
  - It is associated with ureteral or ureteropelvic atresia
  - The affected kidney is nonfunctional
  - Frequently, it is associated with contralateral abnormalities, especially ureteropelvic junction obstruction.
- Dysplasia of the renal parenchyma is seen with urethral obstruction or reflux present early in pregnancy, or obstructed ureter.

1.3.5 Polycystic Kidney Disease

- Polycystic kidney disease, also known as polycystic kidney syndrome is a genetic disorder in which abnormal cysts develop and grow in the kidneys.
- It is characterized by multiple cysts typically involving both kidneys.
- About 15–17 % of cases initially present with multiple cysts in one kidney, progressing to bilateral disease in the majority.
- Polycystic kidney disease is one of the most common hereditary diseases.
- It is the cause of nearly 10 % of end-stage renal disease and affects males, and females equally.
- Signs and symptoms of polycystic disease include:
  - High blood pressure
  - Headaches
  - Abdominal pain
  - Hematuria
  - Polyuria
  - Pain in the back
- There are two types of polycystic kidney disease:
  - Autosomal dominant polycystic kidney disease (ADPKD)
  - Autosomal recessive polycystic kidney disease (ARPKD)
- Autosomal dominant polycystic kidney disease (ADPKD):
  - This is the most common of all the inherited cystic kidney diseases
  - The incidence is 1:500 live births
  - It is estimated that about 10 % of end-stage kidney disease (ESKD) patients being treated with dialysis were initially diagnosed and treated for ADPKD.
- There are three genetic mutations with similar phenotypical presentation:
  - PKD-1
  - PKD-2
  - PKD3
- Gene PKD1 is located on chromosome 16 and codes for a protein involved in regulation of cell cycle and intracellular calcium transport in epithelial cells.
- Gene PKD1 is responsible for 85 % of the cases of ADPKD.
- Gene PKD2 is located on chromosome 4 and codes for a group of voltage-linked calcium channels.



Figs. 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 1.10, 1.11, and 1.12 Abdominal CT-scans and intraoperative photographs showing multicystic dysplastic kidneys. Note the different sizes and shapes of these cysts. Note also the total absence of the ureter is some of them while the ureter is small atretic or underdeveloped



Figs. 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 1.10, 1.11, and 1.12 (continued)

- Gene PKD3 is recently discovered third gene.
- It is estimated that less than 10 % of cases of ADPKD appear in non-ADPKD families.
- Cyst formation begins in utero and as the cysts accumulate fluid, they enlarge, separate entirely from the nephron, compress the neighboring kidney parenchyma, and progressively compromise kidney function.

1.3.5.1 Autosomal Recessive Polycystic Kidney Disease (ARPKD)

- This is the lesser common of the two types of PKD, with an incidence of 1:20,000 live births.
- It is typically diagnosed in the first few weeks after birth.
- Unfortunately, the kidneys are often underdeveloped resulting in a 30 % death rate in newborns with ARPKD.
- ADPKD individuals might have a normal life; conversely, ARPKD can cause kidney dysfunction and can lead to kidney failure by the age of 40–60.
- ADPKD1 and ADPKD2 are very different, in that ADPKD2 is much milder.
- Currently, there are no therapies proven effective to prevent the progression polycystic kidney disease (autosomal dominant).

1.3.6 Simple (Solitary) Renal Cyst

- Numerous renal cysts are seen in the cystic kidney diseases, which include polycystic kidney disease and medullary sponge kidney.
- Simple renal cysts are different from these cysts.
- A renal cyst is an abnormal fluid collection in the kidney.
- Simple kidney cysts do not enlarge the kidneys, replace their normal structure, or cause reduced kidney function like PKD.
- Significant renal damage is rare in these cysts and usually only requires continuous follow-up and no surgical interventions.
- There are several types of renal cysts based on the Bosniak classification.
- The Bosniak classification categorizes renal cysts into five groups.
  - Category I:
    - Benign simple cyst with thin wall without septa, calcifications, or solid components.
    - It does not enhance with contrast, and has a density equal to that of water.
  - Category II:
    - Benign cyst with a few thin septa, which may contain fine calcifications or a small segment of mildly thickened calcification.
    - This includes homogenous, high-attenuation lesions less than 3 cm with sharp margins but without enhancement.
    - Hyperdense cysts must be exophytic with at least 75 % of its wall outside the kidney to allow for appropriate assessment of margins, otherwise they are categorized as IIF.
  - Category IIF:
    - Up to 5 % of these cysts are malignant and as such they require follow-up imaging, though there is no consensus recommendation on the appropriate interval of follow up.
    - Well marginated cysts with a number of thin septa, with or without mild enhancement or thickening of septa.
    - Calcifications may be present; these may be thick and nodular. There are no enhancing soft tissue components.
    - This also includes nonenhancing high-attenuation lesions that are completely contained within the kidney and are 3 cm or larger.
  - Category III:
    - Indeterminate cystic masses with thickened irregular septa with enhancement.
    - 50 % of these lesions are ultimately found to be malignant.
  - Category IV:
    - Malignant cystic masses with all the characteristics of category III lesions but also with enhancing soft tissue components independent of but adjacent to the septa.
    - 100 % of these lesions are malignant.
- The majority are benign, simple cysts that can be monitored. However, some are cancerous or are suspicious for cancer and these are removed.
- Simple renal cysts are more common as people age. An estimated 25 % of people 40 years of age and 50 % of people 50 years of age have simple kidney cysts.
- The cause of simple kidney cysts is not fully understood and several theories were proposed.
  - Obstruction of tubules
  - Deficiency of blood supply to the kidneys may play a role.
  - Diverticula sacs that form on the tubules, may detach and become simple kidney cysts.
- Simple kidney cysts usually do not cause symptoms or negatively affect the kidneys.
- In some cases, however, pain can develop when cysts enlarge and press on other organs.
- Most simple kidney cysts are found during imaging tests done for other reasons.
- Sometimes cysts become infected, causing fever, pain, and tenderness.
- Some studies have found a relationship between simple kidney cysts and high blood pressure.

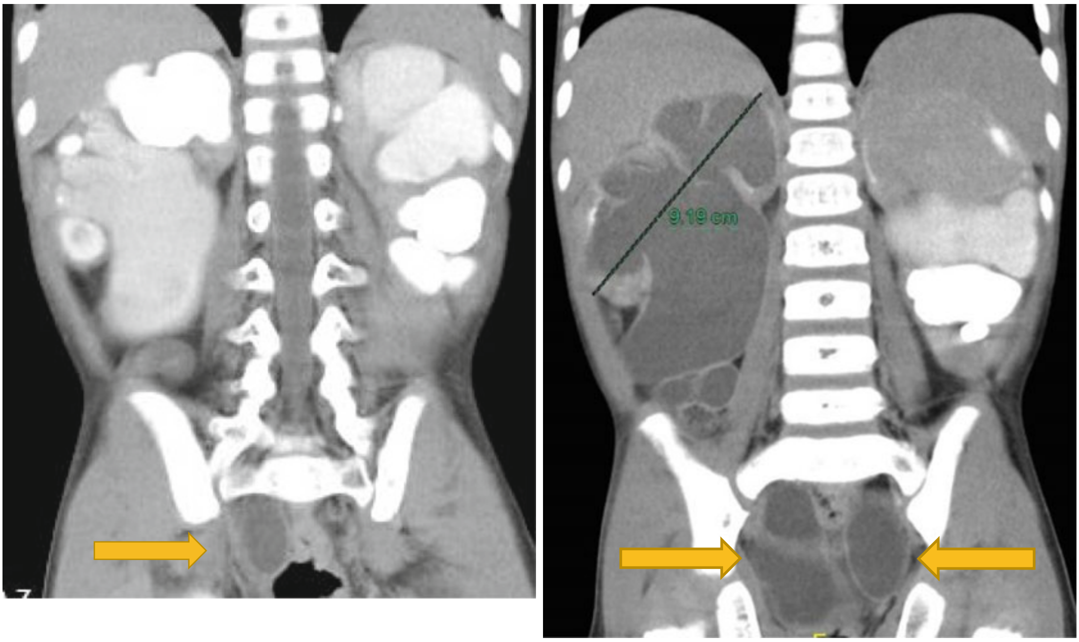
- When a cyst is found, the following imaging tests can be used to differentiate between simple and complicated renal cysts.
  - Abdominal ultrasound
  - CT-scan
  - MRI
- Simple renal cysts that do not cause any symptoms require no treatment and can be monitored with periodic ultrasounds.
- Symptomatic simple renal cysts can be treated with ultrasound guided sclerotherapy.
- Large symptomatic simple renal cysts can be drained and deroofed laparoscopically.
- Parapelvic cysts:
  - Parapelvic cysts originate from around the kidney at the adjacent renal parenchyma, and plunge into the renal sinus.
- Peripelvic cysts:
  - Peripelvic cysts are contained entirely within the renal sinus, possibly related to dilated lymphatic channels.
  - They can mimic hydronephrosis when viewed on CT in absence of contrast.

1.3.7 Renal Fusion and Renal Ectopia

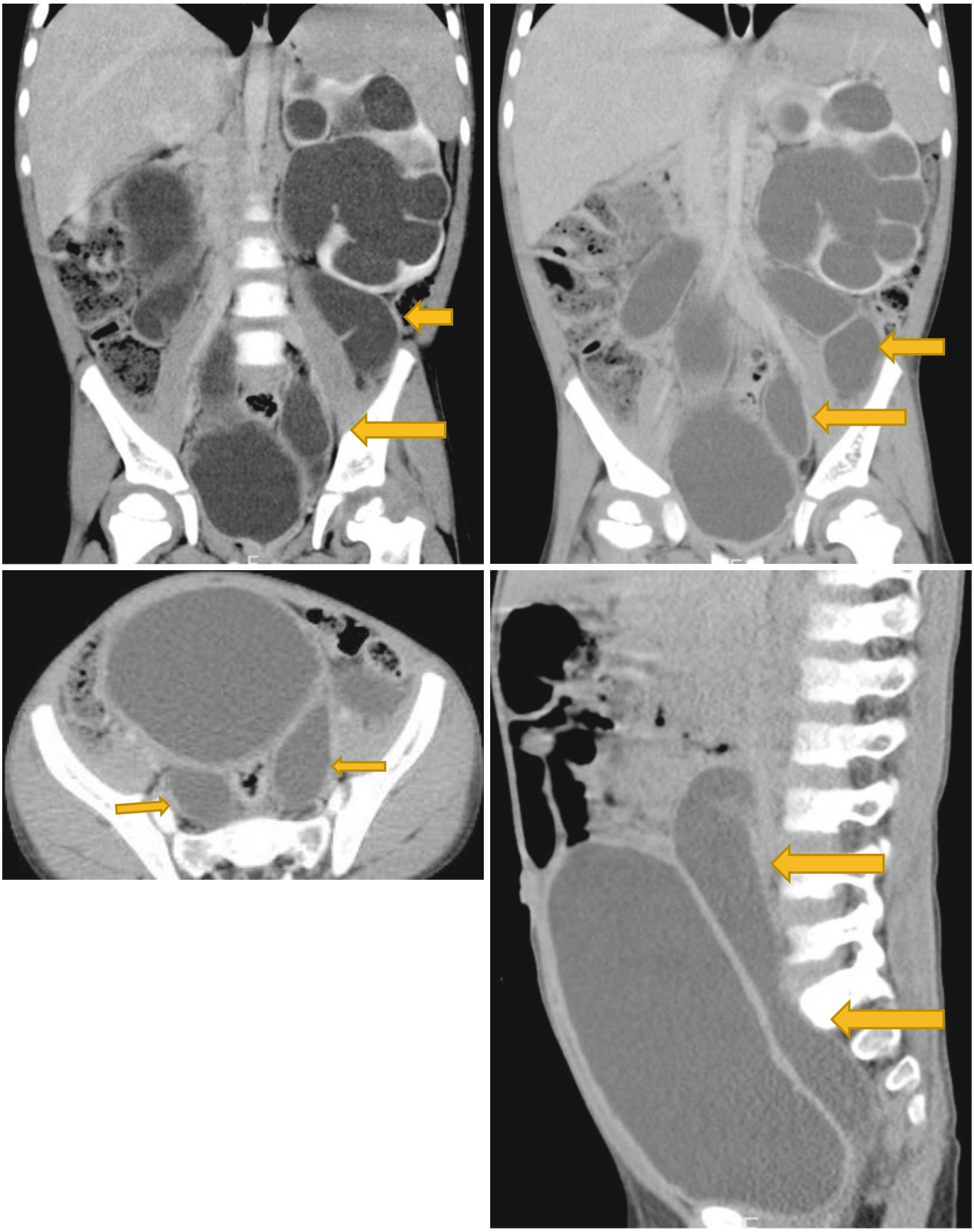
- Renal ectopy and fusion are common congenital anomalies of the kidney and urinary tract, and result from disruption of the normal embryologic migration of the kidneys.
- Although children with these anomalies are generally asymptomatic, some children develop symptoms due to complications, such as infection, renal calculi, and urinary obstruction (Figs. 1.13, 1.14, 1.15, 1.16, 1.17, and 1.18).
- The most frequent abnormality seen is a horseshoe kidney containing two excretory systems and two ureters.
- They are usually asymptomatic but are prone to obstruction.

1.3.8 Horseshoe Kidney

- A horseshoe kidney is formed by fusion across the midline of two distinct functioning kidneys, one on each side of the midline.



Figs. 1.13 and 1.14 CT-urography showing bilateral duplex kidney with hydroueters. Note the associated hydronephrosis and the massively dilated ureters



Figs. 1.15, 1.16, 1.17, and 1.18 CT-urography showing duplex kidneys with hydronephrosis and hydroureters

- They are connected by an isthmus of either functioning renal parenchyma or fibrous tissue.
- In the vast majority of cases the fusion is between the lower poles (90 %).
- In the remainder the superior or both the superior or inferior poles are fused. This latter configuration is referred to as a sigmoid kidney.
  - The kidneys develop in the pelvis and migrate up to their final position in the retroperitoneal space in the lumbar region.
- Prior to their ascent, the renal capsule has not matured and the kidneys still lie within the pelvis.
- It is suggested that abnormal flexion or growth of the developing spine and pelvic organs brings the immature kidneys together for a longer period than usual, leading to fusion of the two renal elements and hence forming the so-called horseshoe kidney.
- As this abnormal fusion occurs in the pelvis, the subsequent kidney cannot undergo normal migration and rotation.
- In the normal kidneys, the lower poles of the kidneys rotate laterally. However, with a horseshoe kidney, these poles remain medially positioned.
- The horseshoe kidney cannot migrate to the usual position because the fusion will not allow passage by the inferior mesenteric artery.
- Horseshoed kidney is the most common type of fusion anomaly.
- For the most part, the horseshoe kidney functions as a normal kidney. Many times, kidney malformations are accompanied by lower urinary tract anomalies as well.
- With horseshoe kidney, the kidneys can be located anywhere along the normal embryologic ascent of the kidneys.
- In 90 % of cases, the fusion of the kidneys occurs in the lower poles. In this condition, both kidneys are malrotated and their lower poles are joined.
- The collection system of a horseshoe kidney is usually deviated inwards at the lower poles because of the fusion with the isthmus.
- The ureters arise from the kidneys anterior rather than medially.
- The ureter also has a higher insertion point into the renal pelvis than that of a normal kidney.
- The blood supply to the horseshoe kidney is also different than most kidneys. There is actually several different ways that it can receive its supply. The blood supply could arise from the aorta, the iliac arteries and the inferior mesenteric artery. And it could occur as one of these, or a combination of all of them. Although in 65 % of the cases, the isthmus is supplied by single vessel from the aorta.
- It has been estimated that 22–24.8 % of patients with horseshoe kidney also have a renal vein anomaly as well. The most common of these is multiple right renal veins.
- The kidneys are joined by an isthmus which links the lower poles in 95 % of cases and the upper poles in 5 %.
- The isthmus may be fibrotic, dysplastic, or normal renal parenchyma.
- The position of the isthmus is variable.
- The isthmus lies at level of L4 just below the origin of the inferior mesenteric artery (IMA) in 40 %.
- The presence of the IMA may restrict further ascent of the horseshoe during early embryogenesis.
- In another 40 % the kidneys the isthmus is located in a normal anatomical position, whilst the kidneys lie lower in the pelvis in the remaining 20 %.
- Malrotation of the kidneys is always present and is attributed to early fusion prior to normal rotation.
- The renal pelvices remain anterior, with the ureters crossing the isthmus.
- The blood supply to horseshoe kidneys is extremely variable.
  - Thirty percent have a normal anatomical pattern
  - The remaining 70 % are supplied by a combination of vessels entering from the aorta or the renal, mesenteric, iliac, or sacral arteries.
  - The isthmus frequently has separate blood vessels that may occasionally represent the entire renal blood supply.

- Horseshoe kidneys are susceptible to trauma and are an independent risk factor for the development of renal calculi and transitional cell carcinoma of the renal pelvis.
- Horseshoe kidneys are found in approximately 1 in 400–500 adults.
- They are more frequently encountered in males (M:F 2:1).
- The vast majority of cases are sporadic, except for those associated with genetic syndromes.
- Horseshoe kidneys are frequently associated with both genitourinary and non-genitourinary malformations.
- Chromosomal/aneupliodic anomalies:
  - Down syndrome
  - Turner syndrome: up to 7 % have a horseshoe kidney
  - Edward syndrome (trisomy 18): up to 20 % have a horseshoe kidney
  - Patau syndrome (trisomy 13)
- Non-aneupliodic anomalies
  - Ellis-van Creveld syndrome
  - Fanconi anaemia
  - Goltz syndrome
  - Kabuki syndrome
  - Pallister-Hall syndrome
  - VACTERL association
- Horseshoe kidneys are asymptomatic and usually identified incidentally.
- They are however prone to a number of complications including:
  - Hydronephrosis, secondary to pelviureteric junction obstruction
  - Renal calculi
  - Increased susceptibility to trauma
  - Infection and pyeloureteritis cystica
  - Increased incidence of malignancy
    - Wilms tumour
    - Transitional cell carcinoma
    - Renal carcinoid
  - Renovascular hypertension
- Associated abnormalities:
  - It has been reported that one third of patients with horseshoe kidney have at least one other abnormality.
  - The most commonly affected systems are the gastrointestinal, skeletal, cardiovascular and central nervous system.
  - Ureteral duplication is reported to occur in 10 %
  - VUR is reported to occur in 10–80 %.
  - Multicystic dysplasia and autosomal dominant polycystic kidney disease has also been reported.
  - Horseshoe kidney is present in 21 % of patients with trisomy 18 and in 7 % in those with Turner's syndrome.
  - Abdominal aortic aneurysms have been reported later in life .
  - Hypospadias and cryptorchidism occurs in 4 % of males and bicornate uterus or septate vagina in 7 % of females.
- Outcomes depend on associated urological problems as horseshoe kidneys are usually asymptomatic.
- PUJ obstruction occurs in 30 % and is more often left-sided.
- Renal calculi occur in up to 20 % of horseshoe kidneys.
- Xanthogranulomatous pyelonephritis has been reported but is rare.
- There is an increased risk of malignancy in horseshoe kidneys in childhood.
  - Wilms tumor occurs with a 1.5- to 8-fold increased risk and surgical management can be challenging.
  - Renal cell carcinoma, transitional cell carcinoma, oncocytoma and carcinoid have all been described.
- The diagnosis of horseshoe kidney can be confirmed by ultrasound, intravenous urography and CT-scan/MRI.
- Horseshoe kidneys in themselves do not require any treatment, and patients have normal life expectancy.
- It is however important to recognize their presence prior to abdominal surgery or renal intervention for one of their many complications.

1.3.9 Crossed Fused Renal Ectopia

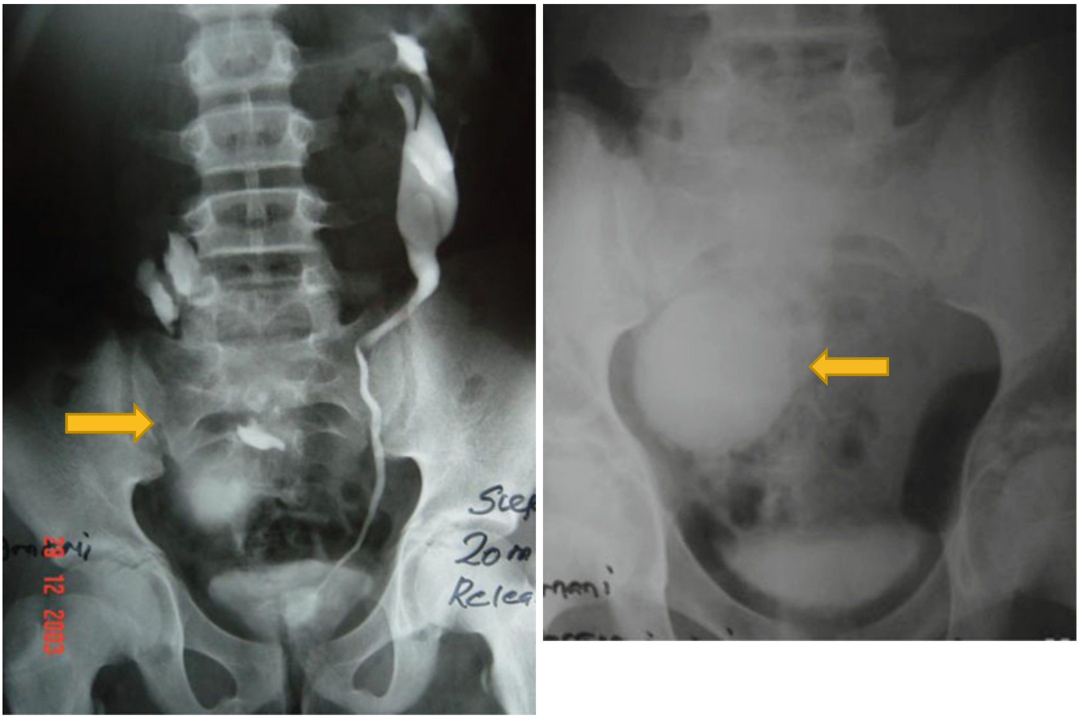
- The second most common fusion anomaly is crossed renal ectopia.

- Crossed fused renal ectopia refers to an anomaly where the kidneys are fused and located on the same side of the midline.
- If during ascent, one kidney advances slightly ahead of the other, the inferior pole of one may come into contact with the superior pole of the lower kidney and fuse, resulting in crossed fused renal ectopia.
- The exact cause of this is not fully understood.
    - Some evidence supports that an abnormally situated umbilical artery prevents normal cephalic migration.
    - Another theory is that the ureteric bud crosses to the opposite side and induces nephron formation in the contralateral metanephric blastema. The result is a single renal mass with two collecting systems being located on one side of the abdomen.
- The estimated incidence is around 1 out of 7,000 births.
- It is more common in males than females with a M:F ratio of 2:1 .
- In crossed renal ectopia, both kidneys are located on the same side and may occur with:
    - Fusion (85 %)
    - Without fusion (<10 %)
    - Extremely rare it can be solitary or bilateral
    - The left kidney is three times more likely to migrate to the right than vice versa.
    - Other fusion anomalies are extremely rare and include lump kidney, sigmoid kidney, disk kidney and L-shaped kidney.
    - There are rare cases of familial crossed ectopia.
- The upper pole of the crossed kidney usually fuses to the lower pole of the normally positioned kidney.
- The kidney usually remains incompletely rotated with the pelvis anterior. However, if complete rotation occurs prior to fusion, an S- or sigmoid kidney results and the pelvices face in opposite directions.
- The lump or disk kidney results from extensive fusion of the developing kidneys.
- In the 'L' shaped kidney, the crossed kidney assumes a transverse position.
- The vascular supply of fused kidneys is extremely variable. There may be anomalous branches to both kidneys arising from the aorta or common iliac artery.
- Rarely the renal artery crosses the midline to supply the crossed kidney.
- Urinary drainage is usually by separate ureters entering the bladder on either side of the trigone.
- Most crossed kidneys are asymptomatic and remain undetected throughout life.
- However they may present with infection, a mass or on screening for urinary abnormalities .
- More than 90 % of crossed renal ectopia results in renal fusion.
- Subtypes:
    - Type a: inferior crossed fusion
    - Type b: sigmoid kidney
    - Type c: lump kidney
    - Type d: disc kidney
    - Type e: L-shaped kidney
    - Type f: superiorly crossed fused
- Crossed fused renal ectopia is more common on the left side (Left-to-right ectopy is 3:1).
- In 90 % of crossed ectopy, there is at least partial fusion of the kidneys (the remainder demonstrate two discrete kidneys on the same side, crossed-unfused ectopy).
- In a crossed fused renal ectopic kidney, complications such as nephrolithiasis, infection, and hydronephrosis approaches 50 %.
- Crossed fused renal ectopia usually doesn't require any primary treatment.
- It is important to diagnose crossed fused renal ectopia prior to any surgical intervention.
- The blood supply to cross-fused kidney is usually anomalous and angiography is recommended before surgical intervention.
- The diagnosis can be confirmed with CT-scan, MRU and isotope scanning.
- There is an increased incidence of associated malformations including cardiac, musculoskeletal, genital, gastrointestinal, anorectal, and renal systems, and occasionally as part of the VACTERL association.
- The most common associated urological abnormality is VUR.

- It has also been described with pelvic malignant lipomatosis and an entire chromosomal translocation involving chromosomes 1 and 6.
- Crossed renal ectopia are usually asymptomatic and require no treatment unless complications develops.
- There is a relatively high incidence of chronic renal disease in crossed renal ectopia, and long term follow up is important.

1.3.10 **Ectopic Kidney** (Figs. 1.19 and 1.20)

- An ectopic kidney results from either incomplete, excess or abnormal ascent of the embryonic kidney.
- Renal ectopia may arise as a result of abnormalities of the ureteric bud or metanephros, an abnormal vascular supply or genetic abnormalities.
- The incidence of renal ectopia in postmortem studies varies from 1 in 500 to 1 in 1,290.
- It occurs slightly more frequently on the left side.
- 10 % of cases are bilateral.
- It affects males and females equally.
- It is prone to obstruction and infection.
- Ectopic kidney is also more prone to trauma.
- Around 50 % remain unrecognized throughout life.
- Ectopic kidneys lie outside the renal fossa and may be located in:
  - The pelvis
  - The iliac fossa
  - The chest
  - Crossed
- Simple renal ectopia refers to a kidney in the ipsilateral retroperitoneal space and is most commonly located in the pelvis but may be opposite the sacrum or below the aortic bifurcation.



Figs. 1.19 and 1.20 Intravenous urography showing a right hydronephrotic pelvic kidney. Note also the partial duplication of the left ureter

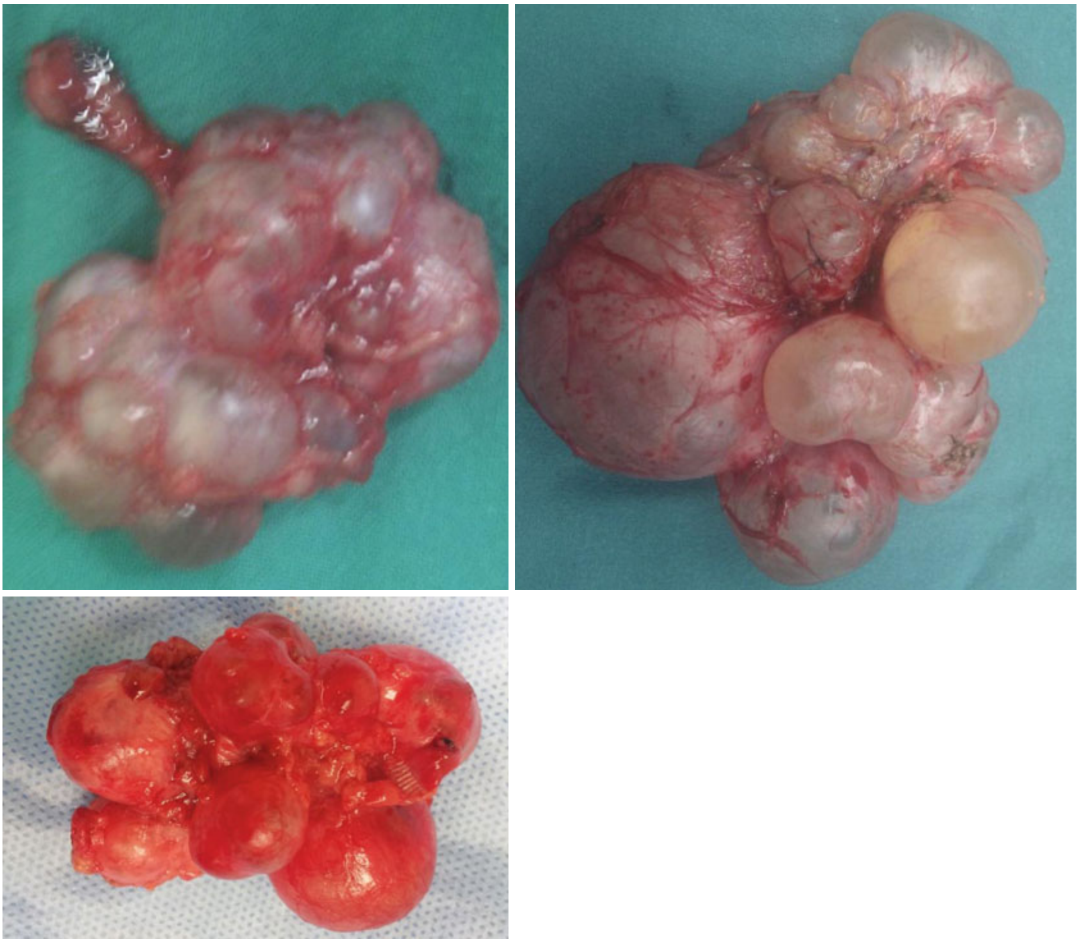
- The lumbar or iliac ectopic kidney is fixed above the iliac crest but below the level of L2 and L3.
- A thoracic kidney is exceedingly rare and is due to excessive cranial migration prior to diaphragmatic closure or delayed closure with continued ascent.
- Ectopic kidneys are rarely normal. They are often small, lobulated kidneys with abnormal rotation with extrarenal calyces and an irregular vascular supply.
- Associated abnormalities:
  - The most common problem associated with an ectopic kidney is vesico-ureteric reflux (VUR) which occurs in up to 85 % of children.
  - Pelvi-ureteric junction (PUJ) obstruction is present in 33–52 %.
  - This is frequently due to a high insertion of the ureter on the renal pelvis, malrotation of the kidney or an anomalous blood supply which obstructs the collecting system.
  - Renal calculi
  - The contralateral kidney is abnormal in as many as 50 % of patients.
  - Contralateral renal agenesis occurs in 10 %.
  - Additional malformations of the cardiovascular, respiratory, genital or skeletal systems are common.
  - Associated skeletal anomalies are most commonly scoliosis and hemivertebrae.
  - Genital malformations in females include duplication of the vagina, bicornuate uterus and hypoplasia or agenesis of the uterus or vagina.
  - The most common genital anomalies in males are hypospadias and cryptorchidism.

Congenital Renal Anomalies

- Renal agenesis
- Renal hypoplasia
- Oligomeganephronia
- Supernumerary kidneys
- Renal dysplasia and multicystic kidney
- Polycystic kidney disease
  - Autosomal dominant polycystic kidney disease (ADPKD)
  - Autosomal recessive polycystic kidney disease (ARPKD)
- Simple (solitary) renal cyst
- Renal fusion and renal ectopia
  - Horseshoe kidney
  - Crossed fused renal ectopia
  - Ectopic kidney
- Pre tumorous conditions (Nephroblastomatosis)
- Tumors presenting in antenatal and early childhood period
  - Mesoblastic nephroma
  - Nephroblastoma
  - Multilocular cystic nephroma
  - Wilms tumor

1.4 Abnormalities of the Ureter

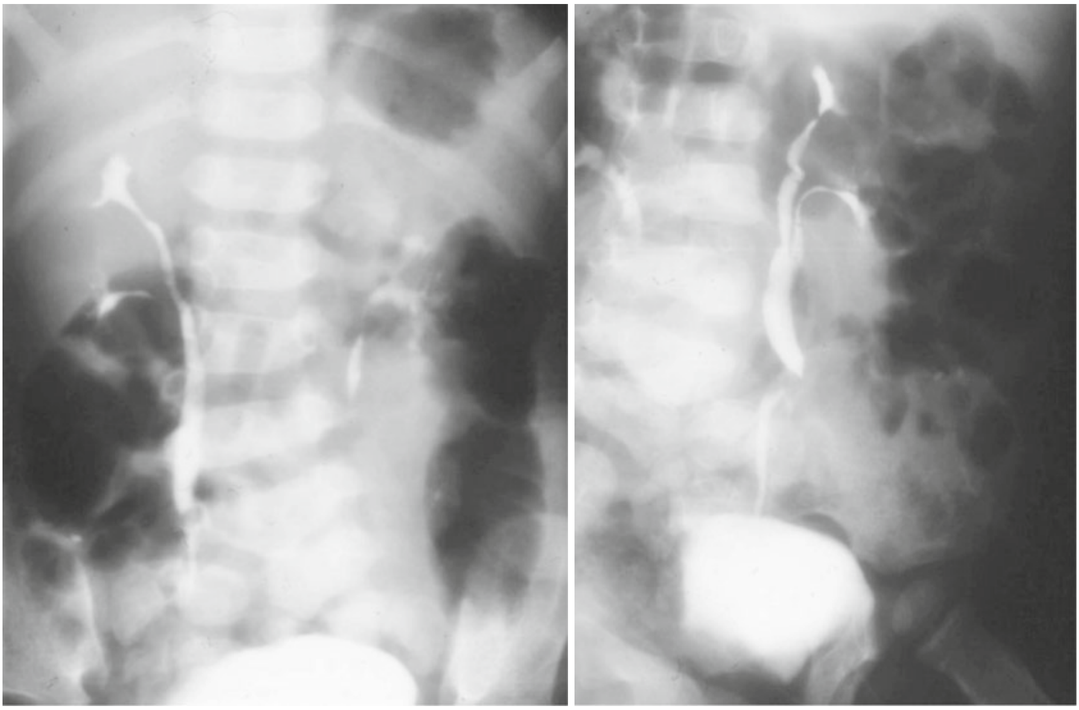
- Ureteral atresia (Figs. 1.21, 1.22, and 1.23):
  - The ureter may be absent or fail to extend to the bladder and end blindly.
  - It is associated with ipsilateral absent or multicystic kidney.
  - Bilateral atresia is incompatible with life.
  - Unilateral atresia is usually asymptomatic but may cause hypertension.
- Duplication of the ureter:
  - This is one of the most common congenital malformations of the urinary tract.
  - Duplicated ureter or Duplex Collecting System is a congenital condition in which the ureteric bud, the embryological origin of the ureter, splits (or arises twice), resulting in two ureters draining a single kidney.
  - It is the most common renal abnormality, occurring in approximately 1 % of the population.
  - The additional ureter may result in a ureterocele, or be an ectopic ureter.
  - It is estimated that duplication of the ureter is found in 0.9 % of a series of autopsies.
  - It is more common in females and is often bilateral.



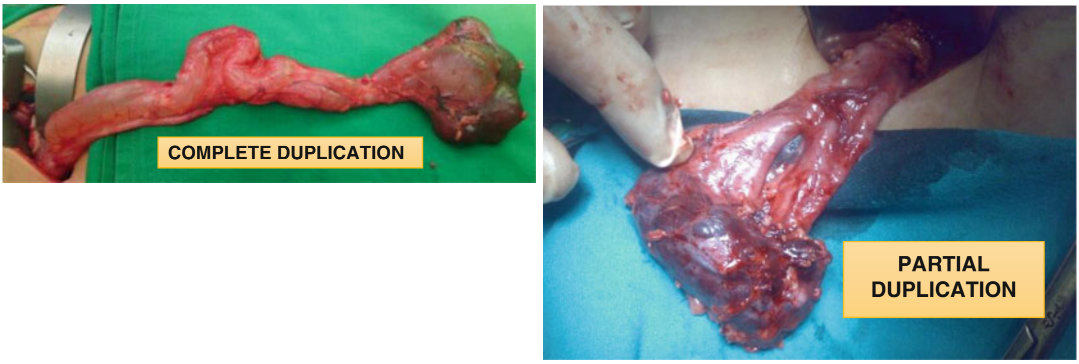
Figs. 1.21, 1.22, and 1.23 Intraoperative photographs showing multicystic dysplastic kidney with ureteric atresia

- Ureteral duplication is divided into two types:
  - Partial ureteral duplication (Figs. 1.24 and 1.25):
- The two ureters drain into the bladder via a single common ureter.
- Partial, or incomplete, ureteral duplication is rarely clinically significant.
  - Complete ureteral duplication (Figs. 1.26 and 1.27):
- The two ureters drain separately.
- Complete ureteral duplication may result in one ureter opening normally into the bladder, and the other being ectopic, ending in the vagina, the urethra or the vulval vestibule.
- These cases occur when the ureteric bud arises twice rather than splitting.
- It is often asymptomatic but commonly presents with persistent or recurrent urinary tract infections.
- Urinary tract infection is most commonly due to vesicoureteral reflux.
- Urinary incontinence in females occurs in cases of ectopic ureter entering the vagina, urethra or vestibule.

- Ureterocele (Figs. 1.28 and 1.29):
  - This is a sacculation of the bladder end of the ureter that can occur either in the bladder or ectopically.
  - It is much more common in girls than in boys.
  - In 10 % of cases it is bilateral.
  - It may be asymptomatic or cause obstruction, incontinence or infection.



Figs. 1.24 and 1.25 Intravenous urography showing partial duplication of the right ureter



Figs. 1.26 and 1.27 Intraoperative photographs showing partial and complete duplication of the ureters

- Ectopic ureteral orifice:
  - This usually occurs with ureterocele and duplication of the ureter.
  - Single ectopic ureters are also seen.
  - Boys may present with recurrent epididymitis, as the ureter drains directly into the vas deferens or seminal vesicle.
  - Girls normally present with incontinence with continual dribbling despite normal voiding.
- Obstruction of the ureteropelvic junction (Figs. 1.30, 1.31, 1.32, 1.33, 1.34, 1.35, 1.36, 1.37, 1.38, and 1.39):
  - This is a common congenital abnormality of the ureter where there is a partial obstruction at the junction between the renal pelvis and upper ureter.
  - The cause of obstruction can be intrinsic or extrinsic.

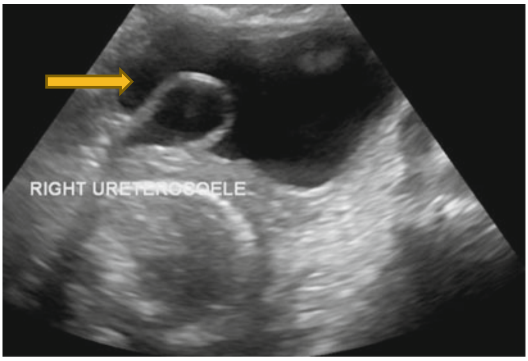


Fig. 1.28 Pelvic ultrasound showing right ureterocele

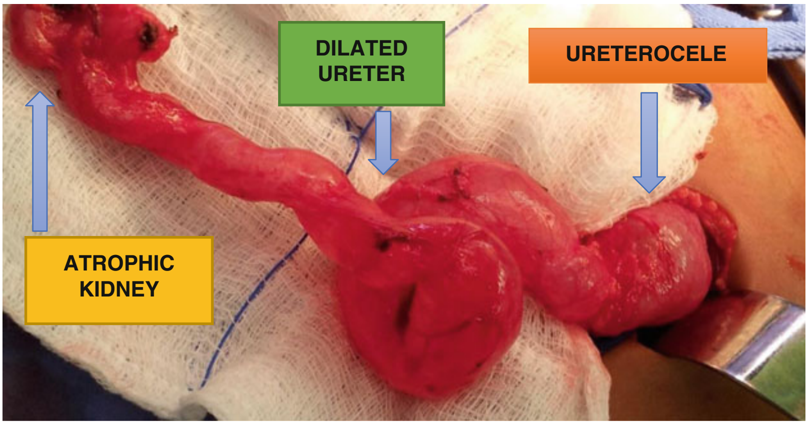
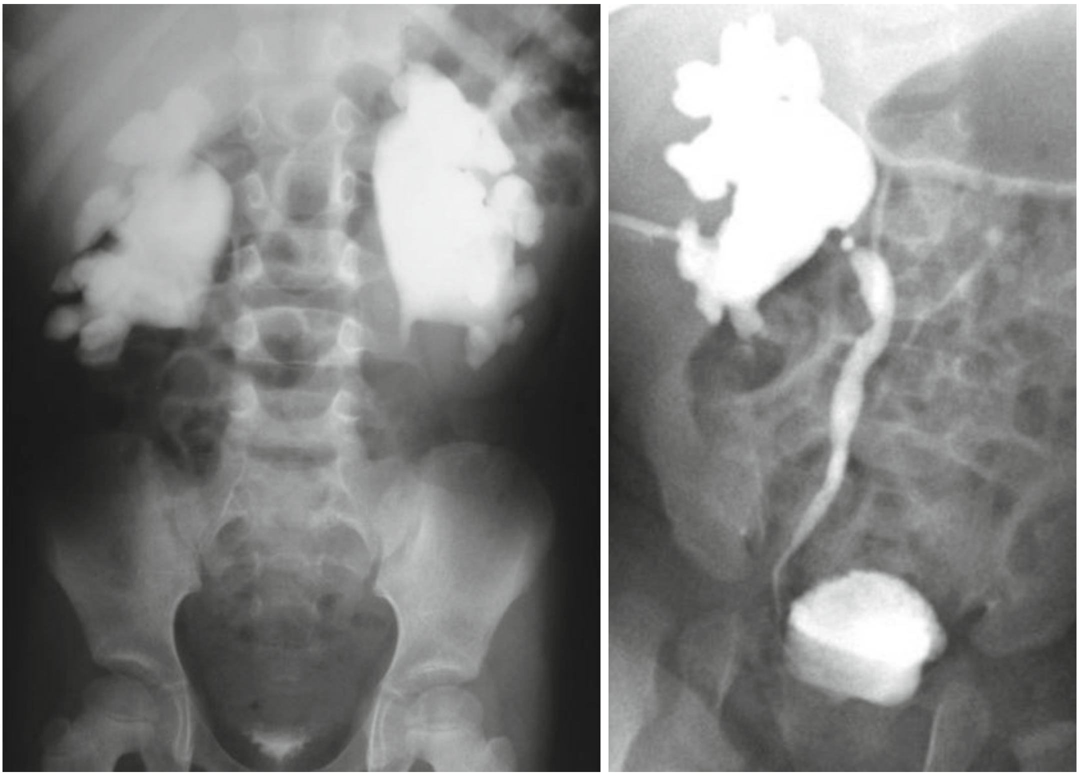


Fig. 1.29 Intraoperative photograph showing an obstructed ureterocele. Note the massively dilated ureter and also the small atrophic kidney

  - Intrinsic obstruction is the commonest and results from localized narrowing at the UPJ junction.
  - A crossing aberrant lower polar vessel is one of the extrinsic causes of UPJ obstruction.
  - It is seen more commonly in boys than in girls.
  - Most cases are unilateral and usually on the left.
  - There are also bilateral cases of UPJ obstruction.
  - The degree of obstruction will determine its effect on the kidneys.
  - With the widespread use of antenatal ultrasound, most of these cases are diagnosed in utero.
  - The presentation is variable depending on the degree of obstruction.
  - Continued severe obstruction will compromise renal function and these cases need to be diagnosed and treated early.
  - The diagnosis can be confirmed with postnatal ultrasound and CT-urography or magnetic resonance urography.
  - The function of the kidney can be assessed with an isotope renogram.
- Obstructed mega-ureter (Figs. 1.40, 1.41, 1.42, 1.43, and 1.44):
  - This is caused by obstruction at the ureterovesical junction.
  - It is four times more common in boys than in girls and is often bilateral.
  - Often, it is associated with absent or dysplastic contralateral kidney.



Figs. 1.30 and 1.31 Intravenous urography showing bilateral hydronephrosis secondary to utero-pelvic junction obstruction (UPJ) and a nephrostogram showing right hydronephrosis secondary to UPJ obstruction

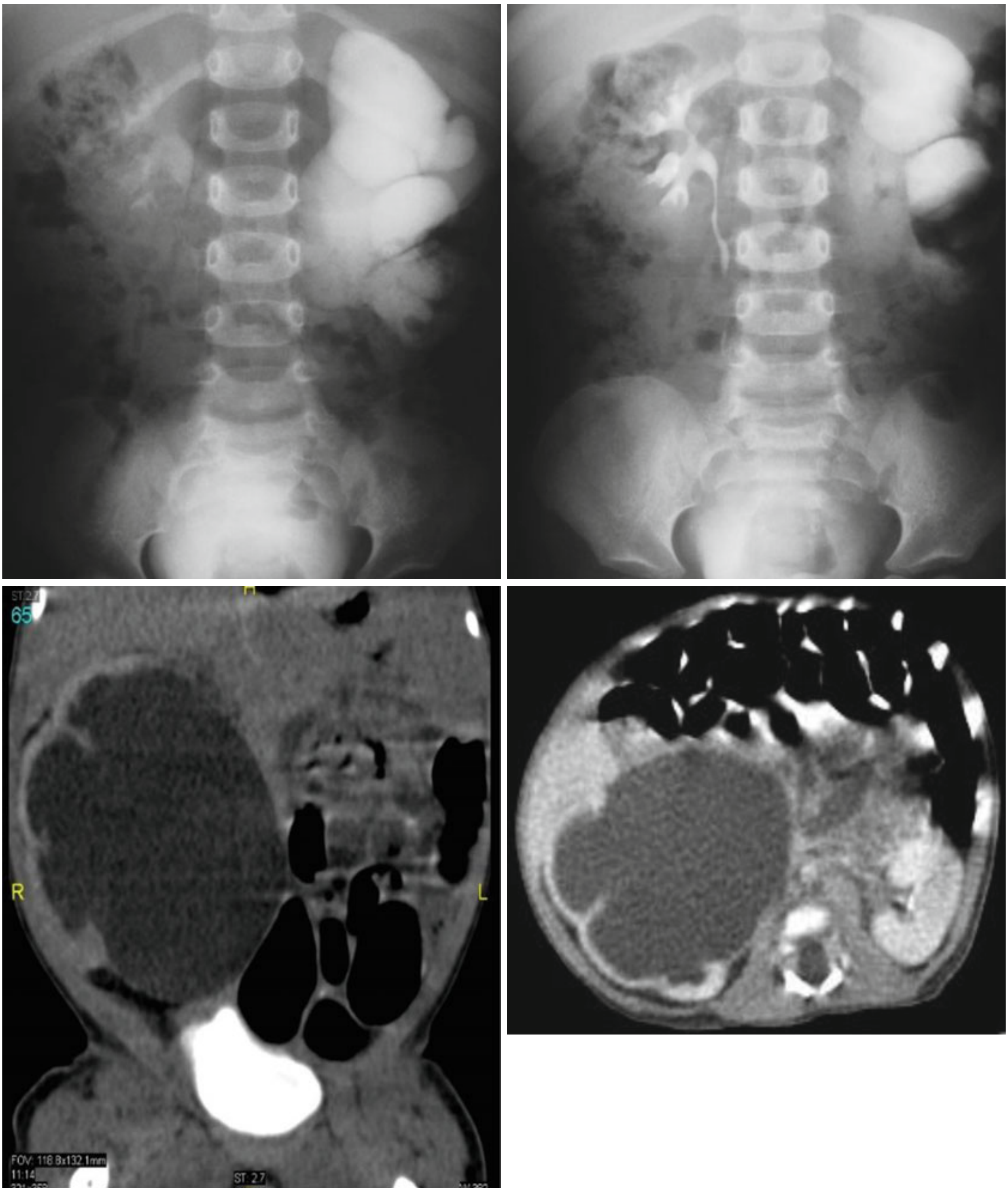
  - Most of these cases are diagnosed using ultrasound.
  - It may be asymptomatic or present with hematuria, recurrent urinary tract infection or abdominal pain.
  - Symptomatic patients are treated with ureteral reimplantation with tapering of the dilated ureter.

Congenital Abnormalities of the Ureter

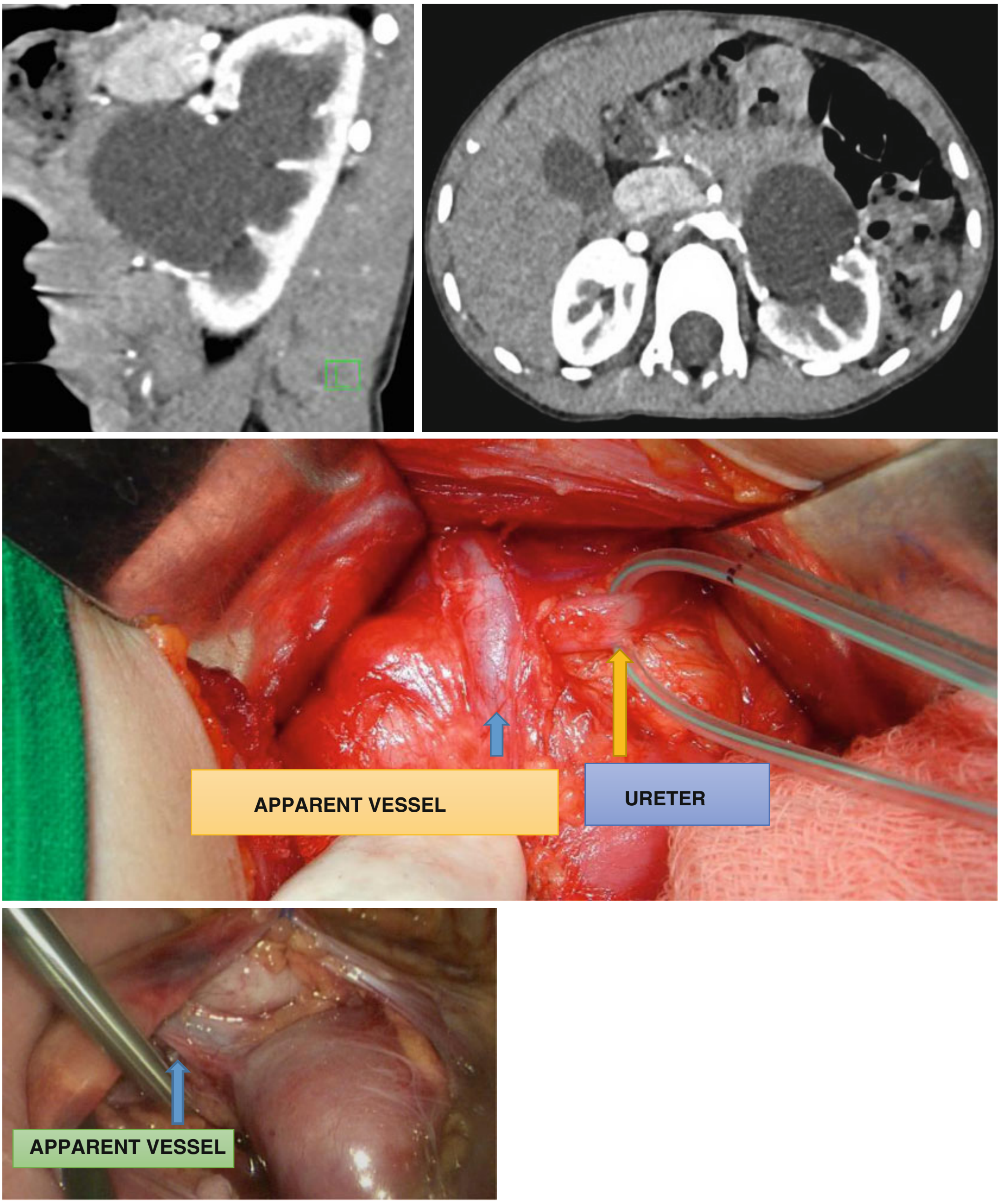
- Ureteral atresia
- Duplication of the ureter
- Ureterocele
- Ectopic ureteral orifice
- Obstruction of the ureteropelvic junction
- Obstructed mega-ureter

1.5 Abnormalities of the Bladder

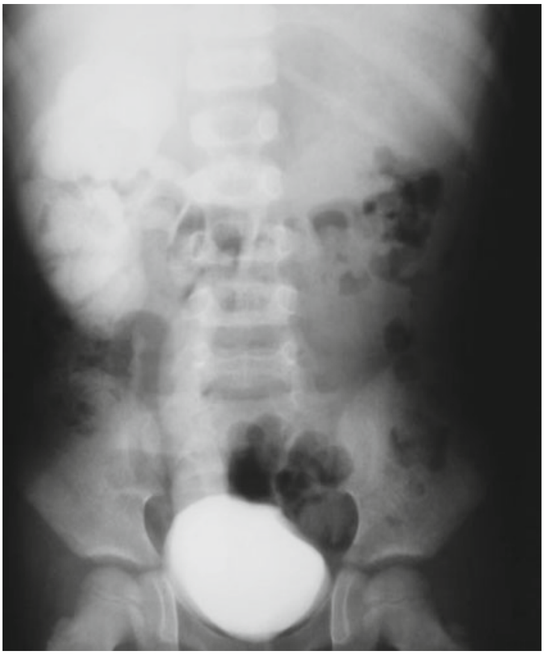
- Bladder Exstrophy (Figs. 1.45, 1.46, and 1.47)
  - This is one of the most severe urological anomalies.
  - It is characterized by absence of the anterior abdominal wall and the wall of the wall of the urinary bladder is open to the outside.
  - It is associated with other abnormalities, especially epispadias.
  - The pubic bones are widely separated.
  - It requires surgical reconstruction.
- Cloacal exstrophy (Figs. 1.48, 1.49, 1.50, and 1.51):

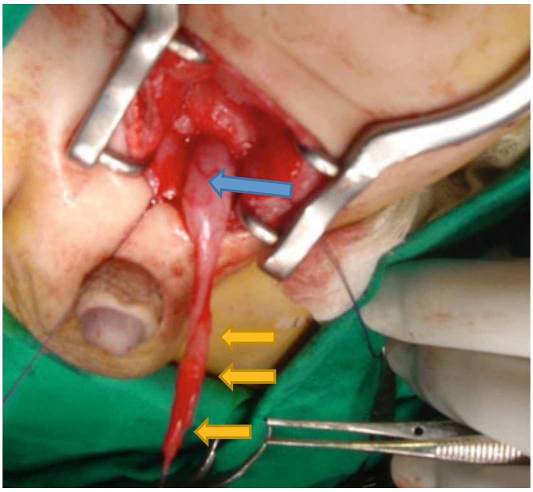


Figs. 1.32, 1.33, 1.34, and 1.35 Intravenous urography and CT-urography showing left and right hydronephrosis. Note the thickness of the renal parenchyma in the CT-urography indicative of sever UPJ obstruction. The function of the kidney in these patients can be assessed with an isoptoe renogram. A split renal function less than 40 % indicate a severe degree of obstruction. This as well as the size of the renal pelvis will determine the urgency of surgical intervention


APPARENT VESSEL
URETER
APPARENT VESSEL

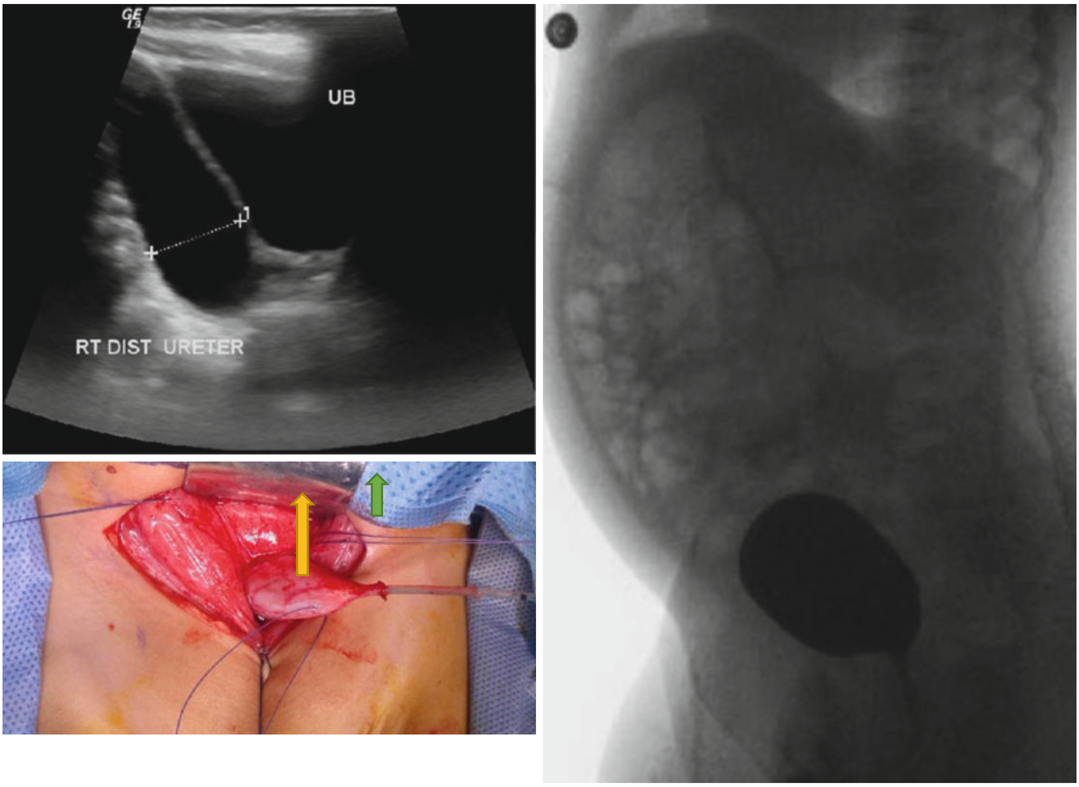
Figs. 1.36, 1.37, 1.38, and 1.39 CT-urography showing hydronephrosis secondary to UPJ obstruction and intraoperative photographs showing apparent lower polar vessels causing pressure and obstruction of the ureter





Figs. 1.40 and 1.41 Intravenous urography showing right megaureter and intraoperative photograph showing reimplantation of a primary megaureter. Note the small caliber of the distal part of the ureter followed by proximal dilatation of the ureter

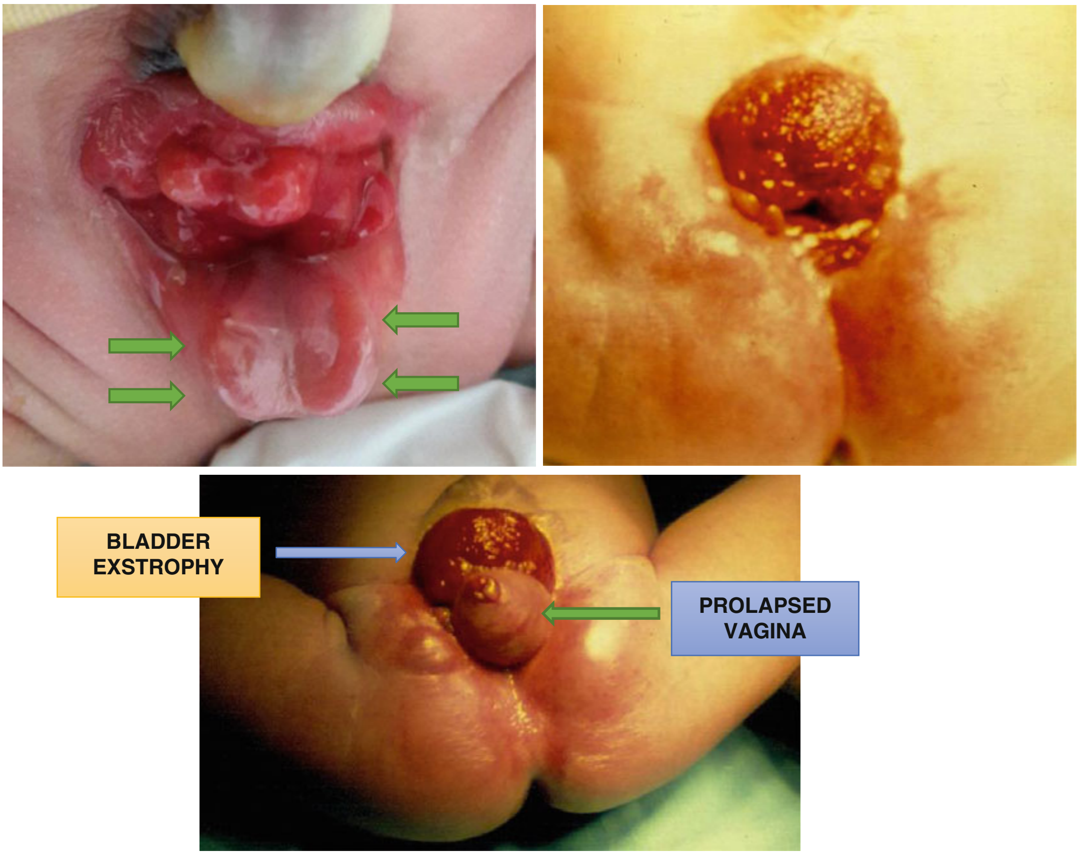
- Cloacal exstrophy is a severe birth defect where the urinary bladder and pat of the intestines are exposed to the outside.
- Cloacal exstrophy is a major birth defect representing the severe end of the spectrum of the exstrophy-epispadias complex.
- It is characterized by the followings:
  - Omphalocele
  - Bladder extrophy (two exstrophied hemibladders separated by a foreshortened hindgut or cecum, often blind-ending resulting in an imperforate anus).
  - Anterior lower abdominal wall defect
  - Widened and separated pubic bones
  - Splitting of both male (penis) and female (clitoris) external genitalia
  - Anorectal agenesis or anteriorly placed anus
  - Spinal defects
- Cloacal exstrophy is an extremely rare birth defect, present in 1/200,000 and 1/400,000 live births.
- The exact pathogenesis of cloacal exstrophy is not known.
  - It is thought that it results from an abnormality during early embryologic development associated with rupture of the cloacal membrane before fusion with the urorectal septum.
  - Genetic and environmental factors may play a role in the etiology.
- Prenatal diagnosis of cloacal exstrophy is possible from ultrasound findings:
  - Non-visualization of the bladder
  - Anterior abdominal wall defect
  - Omphalocele
  - Myelomeningocele
- Omphalocele is found in 88–100 % of patients.
- Gastrointestinal malrotation/duplication and short bowel syndrome are present in 46 %, with absorptive dysfunction in some cases.
- The symphysis pubis is widely separated and the pelvis is often asymmetrically shaped.
- Duplication of the vagina and uterus, as well as vaginal agenesis, has also been reported.



Figs. 1.42, 1.43, and 1.44 Abdominal ultrasound showing a right megaureter and a micturating cystourethrogram showing no reflux. An intraoperative photograph showing reimplantation of the right megaureter. Note the narrow distal ureteric segment and a more dilated proximal ureter

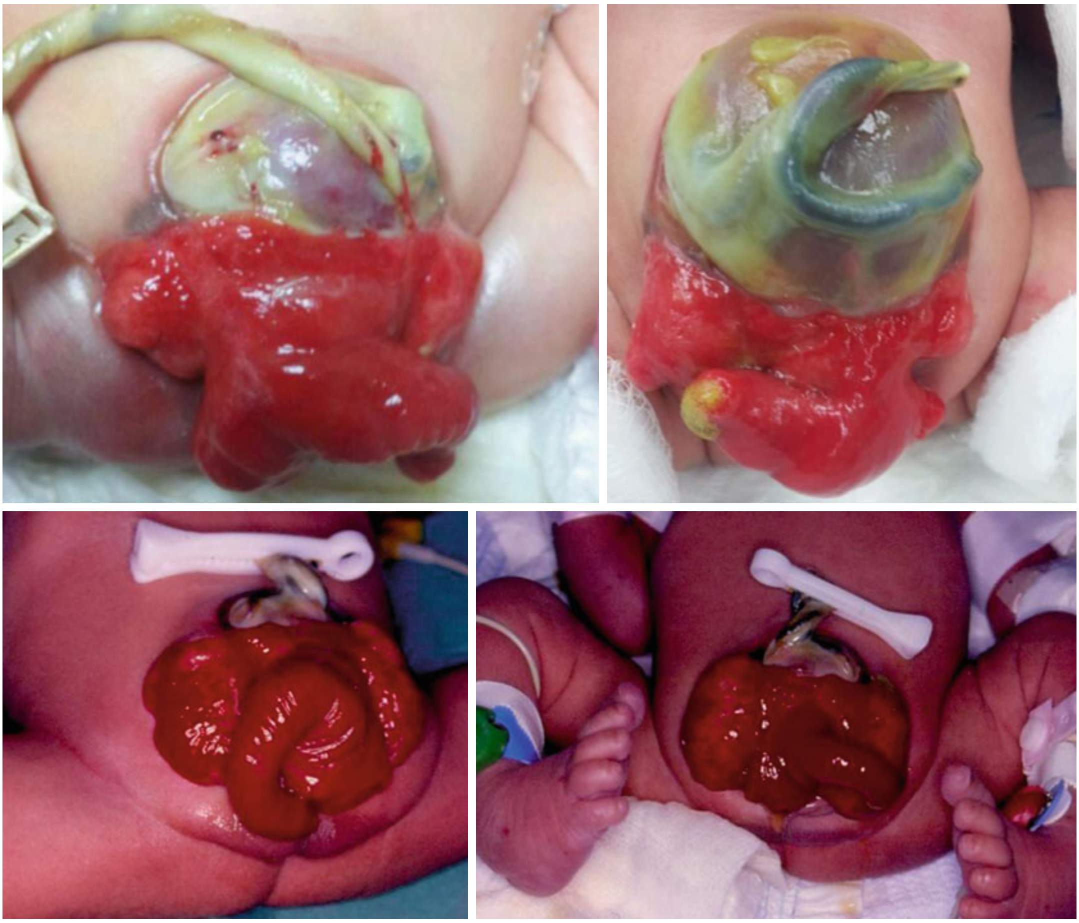
- Various urological malformations may also be present including:
  - Ureteropelvic junction obstruction
  - Ectopic pelvic kidney
  - Horseshoe kidney
  - Renal hypo- or agenesis
  - Megaureter
  - Ureteral ectopy
  - Ureterocele
- Spinal abnormalities ranging from hemivertebra to myelomeningocele occur in most patients and may be accompanied by skeletal and limb anomalies (clubfoot deformities, absence of feet, tibial/fibular deformities, and hip dislocation).
- The diagnosis of cloacal exstrophy is clear clinically and the management of these patients require multidisciplinary team approach.

- Persistent urachus (Figs. 1.52, 1.53, 1.54, 1.55, 1.56, 1.57, 1.58, 1.59, 1.60, and 1.61):
  - The lumen of the allantois, which connects the bladder and the anterior abdominal wall closes normally.
  - Persistent urachus results from failure of this connection to become obliterated.
  - It may appear as a draining umbilical sinus and can become infected.
  - It may appear as fistula connecting the urinary bladder to the umbilicus and the presence of outflow obstruction, urine will be seen coming through the umbilicus.
- Contracture of the bladder neck:
  - This is a common cause of reflux, bladder diverticula and irritable bladder.
- Bladder diverticulum (Figs. 1.62, 1.63, 1.64, 1.65, 1.66, and 1.67):

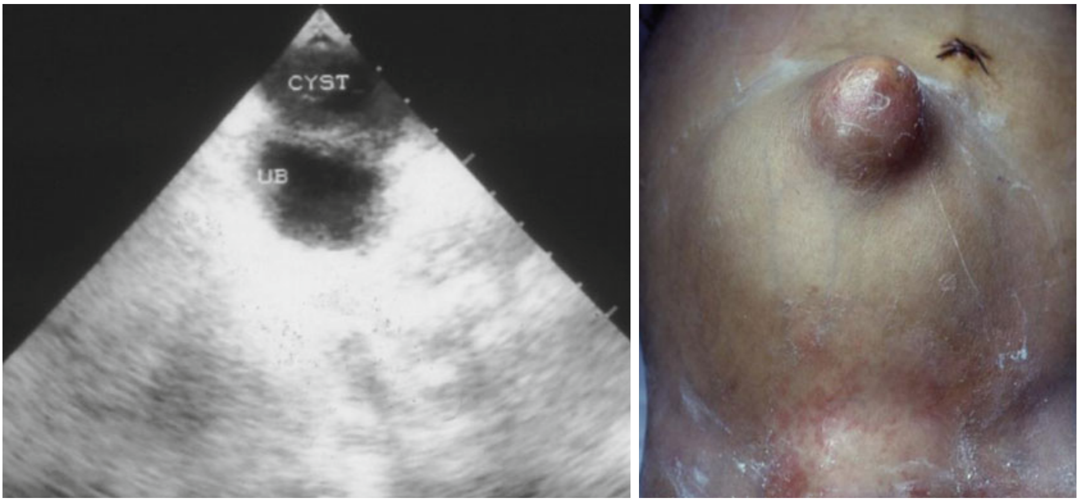


Figs. 1.45, 1.46, and 1.47 Clinical photographs showing bladder exstrophy in a male and two females. Note the associated epispadias in the first one. Note also the granular appearance of the bladder mucosa in the second one and also the associated prolapsed ovary in the third one

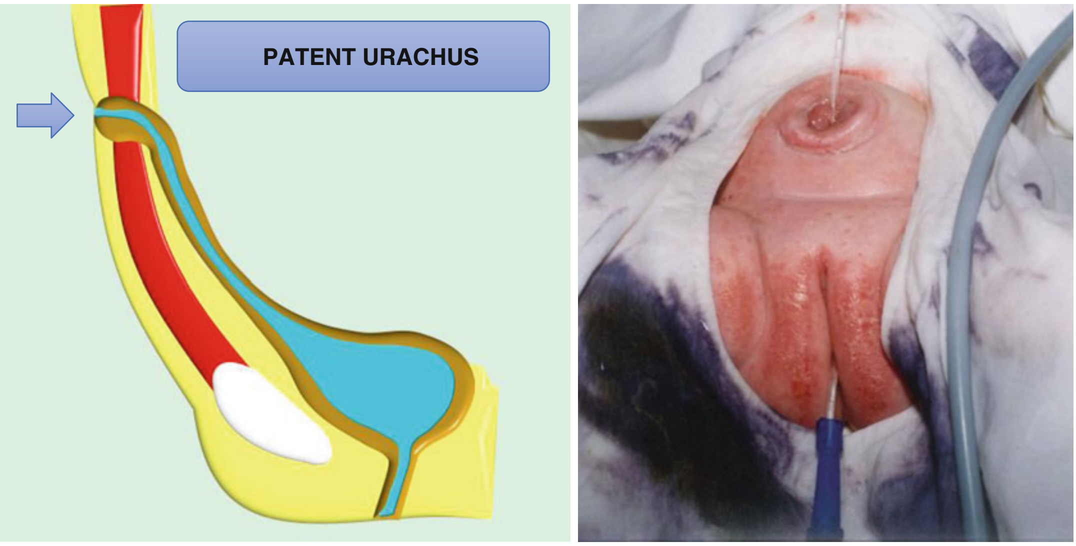
- A bladder diverticulum is an outpouching in the bladder wall. The bladder mucosa herniates through the muscular wall of the urinary bladder.
- It can be either congenital or acquired.
- Acquired bladder diverticula:
  - These are often due to bladder outlet obstruction from an enlarged prostate, urethral stricture or neurologic disease.
  - Acquired diverticula are most typically seen in elderly men and often associated with benign prostatic hyperplasia (BPH).
  - Acquired diverticula are the result of obstruction, infections, or iatrogenic causes.
  - The common causes include:
    - Posterior urethral valves
    - Anterior urethral valves
    - Urethral strictures
    - Neuropathic bladder
    - External sphincter dyssynergy
    - Herniation of the bladder mucosa through the ureteral hiatus after ureteral reimplantation is an iatrogenic cause of bladder diverticulum.
  - They tend to be multiple and occur in trabeculated bladders.
  - Many diverticula that are related to obstruction spontaneously resolve after relief or correction of the obstruction.
  - In some cases, the diverticula that occur in response to obstruction serve a beneficial function by acting as pressure pop-off mechanism, protecting the kidney and ureters from high pressures.



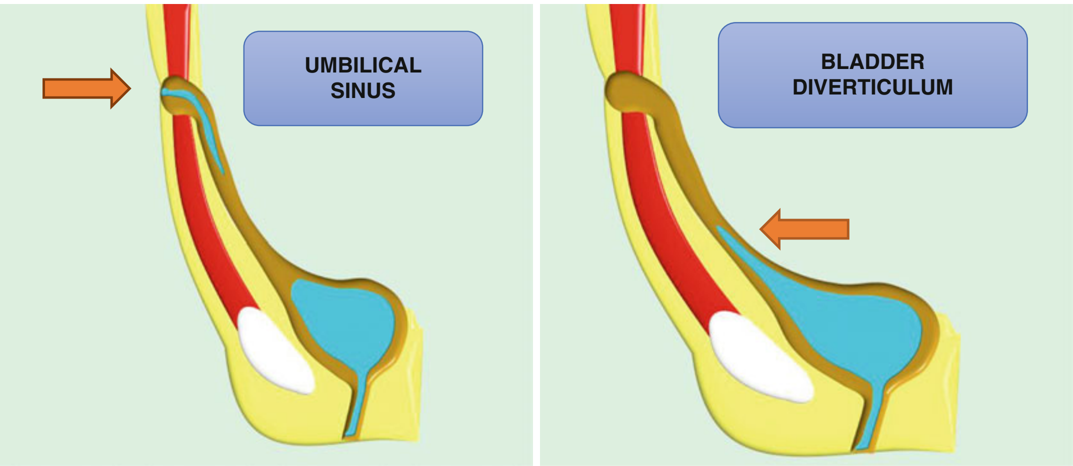
Figs. 1.48, 1.49, 1.50, and 1.51 Clinical photographs showing cloacal exstrophy. Note the associated omphalocele in the first two and absence or very small omphalocele in the second two pictures. Note also the associated club feet in the fourth picture



Figs. 1.52 and 1.53 Abdominal ultrasound showing a cyst infront of the urinary bladder and a clinical photograph showing urachal cyst

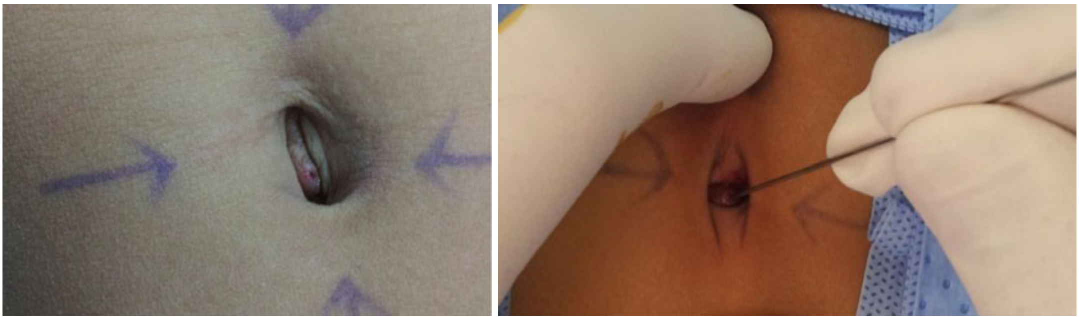


Figs. 1.54 and 1.55 Diagrammatic representation of patent urachus and a clinical photograph of a patient with patent urachus. Note the patent channel connecting the urinary bladder with the anterior abdominal wall at the site of the umbilicus. Note also the feeding tube which was passed from the urethra and passed all the way to the umbilicus via a patent urachus



Figs. 1.56 and 1.57 Diagrammatic representation of an umbilical sinus where the distal part of the urachus remain patent and the rest becomes obliterated. The second diagram represent an obliterated distal part of the urachus while the part attached to the bladder remain patent as a bladder diverticulum

- – Congenital bladder diverticula:
  - These are usually diagnosed in childhood or on prenatal ultrasound.
  - Congenital bladder diverticula have a wide clinical spectrum and could lead to severe kidney damage. Urinary tract infection and urinary retention are the most frequent presentation forms.
  - Some children with diverticula have voiding dysfunction on urodynamic testing. Whether the voiding dysfunction leads to the formation of diverticula



Figs. 1.58 and 1.59 Clinical photographs showing an umbilical sinus. Note the opening in the umbilicus which is discharging. Note the probe which is passed into the sinus for a small distance. Intraoperatively, this was found to be a urachal sinus with the distal part obliterated and connected to the bladder

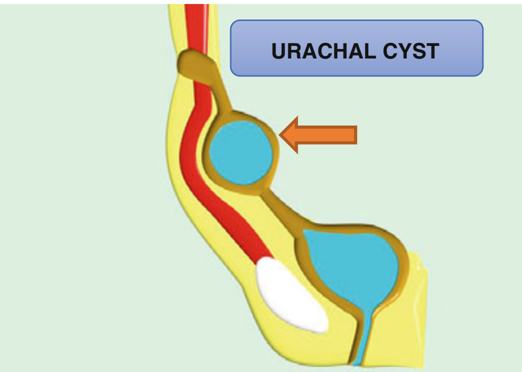


Fig. 1.60 A diagrammatic representation of a urachal cyst

  or the presence of diverticula leads to voiding dysfunction is unclear.
  - Bladder diverticula most commonly occur lateral and superior to the ureteral orifices.
  - They may also occur at the dome of the bladder, particularly in such disorders as bladder outlet obstruction (i.e., posterior urethral valves) or Eagle Barrett syndrome (prune belly syndrome).
  - Congenital deficiency or weakness in the Waldeyer fascial sheath has been implicated as a cause.
  - Congenital diverticula tend to be solitary and are located at the junction of the bladder trigone and detrusor.
  - This location, close to the insertion of the ureter into the bladder, is important because large diverticula can impinge on or distort the ureteral orifices.
  - Diverticular size can vary greatly, with some attaining a size equal to or greater than the volume of the bladder.
  - Diverticula can be wide- or narrow-mouthed.
  - Narrow-mouthed diverticula often empty poorly leading to stasis of urine within diverticula which can be complicated by urinary tract infection, stone formation or epithelial dysplasia.
  - Depending on the size and location, bladder diverticula may cause ureteral obstruction, bladder outlet obstruction, or VUR.
    - Ureteral obstruction is unusual, occurring in approximately 5 % of children with bladder diverticulum.
    - Bladder outlet obstruction is rare.
    - VUR is more common, affecting 8–13 % of patients.
  - Congenital or acquired diverticula do not always require treatment, particularly if they are not associated with urinary infections, bladder stones, or urinary reflux.
  - Bladder diverticula associated with bladder tumors, recurrent infection, or urinary retention do need treatment.
  - Excision of bladder diverticulum can be done through an open or laparoscopic approach.
  - During surgical excision of these diverticula, it is important to avoid ureteral injury due to its close proximity to the diverticulum.
- Bladder ears:
  - Normally, in infants, the bladder assumes a more abdominal position, which places it in close proximity to the internal inguinal ring.

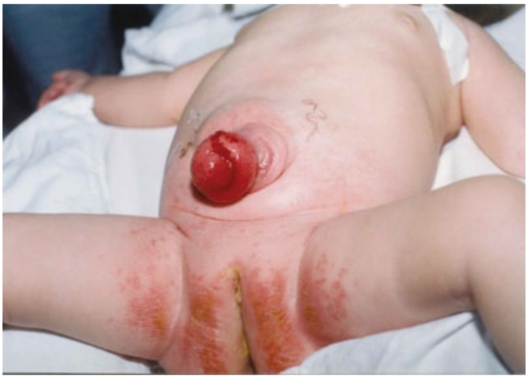


Fig. 1.61 A diagrammatic representation of a patent urachus with prolapse of the mucosa

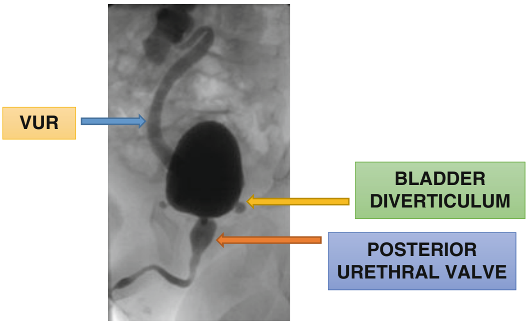
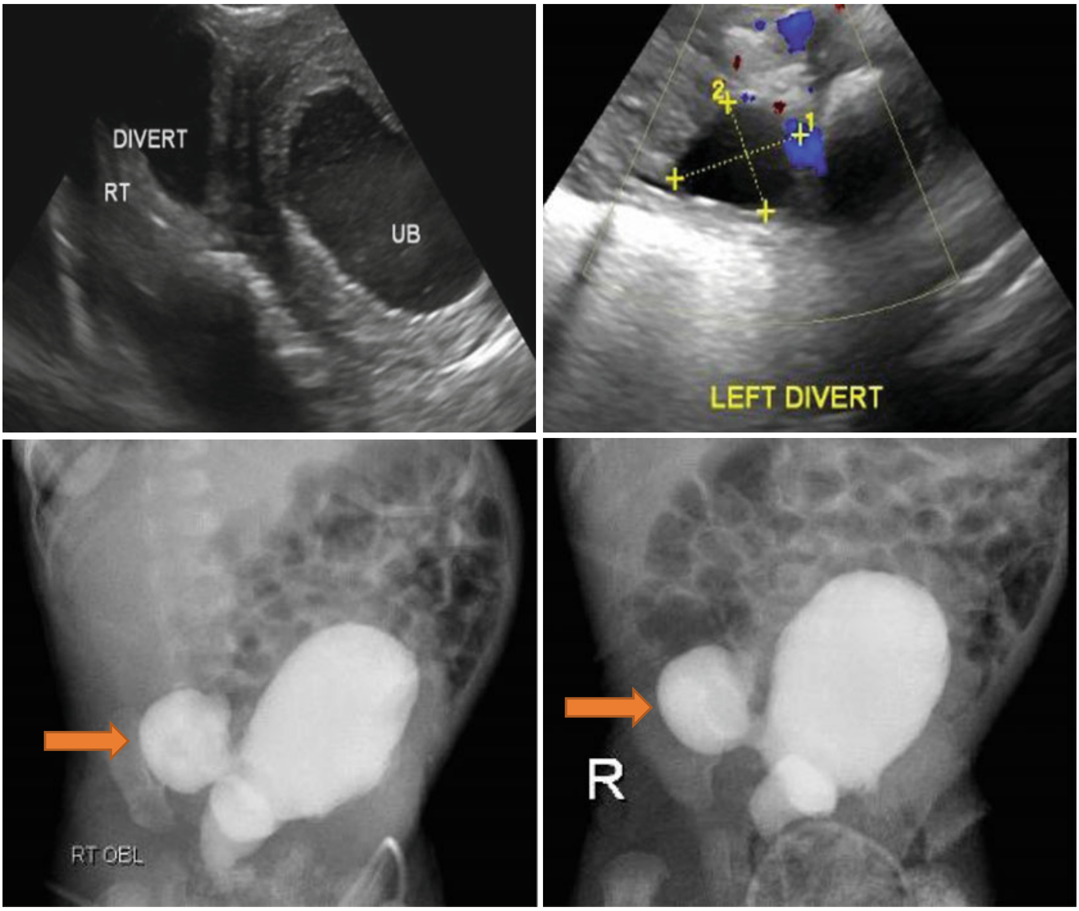

VUR
BLADDER DIVERTICULUM
POSTERIOR URETHRAL VALVE

Fig. 1.62 A micturating cystourethrogram showing posterior urethral valve. Note the associated VUR and bladder diverticulum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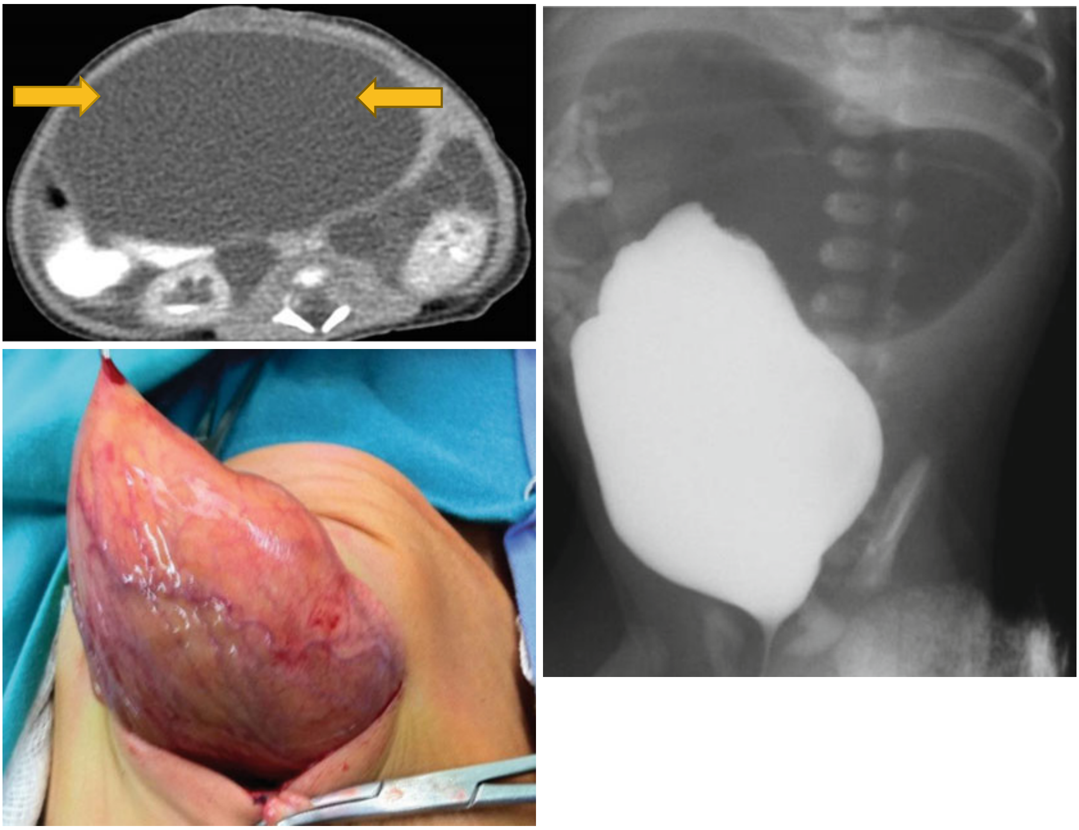
Figs. 1.63, 1.64, 1.65, and 1.66 Pelvic ultrasound and micturating cystourethrogram showing congenital bladder diverticulum. Note the narrow neck of the diverticulum

  - With growth, the pelvis becomes more developed, and the bladder assumes a more pelvic position.
  - Bladder ears are lateral protrusions of the bladder wall through the internal inguinal ring and into the inguinal canal.
  - Bladder ears are rarely seen in adults.
  - Bladder ears are diagnosed using:
    - Voiding cystourethrography (VCUG)
    - Intravenous pyelography (IVP)
    - CT-scan
  - Bladder ears are best seen when the bladder is filled and distended.
  - It is important to recognize and diagnose bladder ears.
  - This is specially so during the repair of inguinal hernia to avoid injury to the bladder which can be mistaken as a large hernia sac.
- Bladder agenesis:
  - Bladder agenesis is a very rare congenital malformation.
  - It is generally incompatible with life.
  - All reported cases were seen in females
  - This is because females have less outlet resistance than males and have preservation of renal function.
  - In bladder agenesis, the ureters may enter into the urethra, vagina, Gartner duct cyst (female), prostatic urethra, rectum, or the patent urachus.
  - Bladder agenesis are often associated with hydroureteronephrosis and renal dysplasia.
  - Other associated anomalies include neurologic, orthopedic, hindgut, and other urogenital anomalies, such as renal agenesis and absence of the prostate, vagina, seminal vesicles, epididymis, or penis.
- Megacystis (Figs. 1.67, 1.68, 1.69, 1.70, and 1.71):
  - Megacystis is an abnormally enlarged urinary bladder.
  - This may result secondary to overfilling of the fetal bladder during development.
  - This can be discovered antenatally on ultrasound or postnatally during evaluation of febrile urinary tract infection.
  - Megacystis is associated with massive high-grade VUR.
  - In the presence of massive reflux, a large percentage of the voiding bladder volume is refluxed into the upper tracts.
  - This causes constant recycling of the urine between the bladder and ureters, resulting in progressive dilation of both.
  - Megacystis can be seen in other conditions, such as:
    - Posterior urethral valves
    - Ehlers-Danlos syndrome
    - Urethral diverticulum
    - Microcolon hypoperistalsis syndrome
    - Sacral meningomyelocele
    - Sacrococcygeal teratoma
    - Pelvic neuroblastoma
- Bladder duplication:
  - Bladder duplication is a very rare malformation.
  - It is divided into two types:
    - Complete bladder duplication
    - Partial bladder duplication
  - Complete bladder duplication is more common than incomplete duplication.
  - With complete bladder duplication, two urethras exist; with incomplete bladder duplication, the bladder joins distally into a single common urethra.
  - The two halves of the bladder are on either side of the midline, with the corresponding ipsilateral ureter draining each bladder half.
  - Associated anomalies occur more commonly in those with complete bladder duplication.
  - These anomalies include:
    - Duplication of the penis, vagina, uterus, lumbar vertebrae, and hindgut.
    - In addition, fistulas may be present between the rectum, vagina, and urethra.
- Bladder septation:
  - Bladder septation anomalies are rare.
  - Fibromuscular or mucosa septations divide the bladder into equal or unequal portions.
  - Septations may be complete or incomplete.
  - The functioning of the associated renal units depends on the adequacy of upper tract drainage.



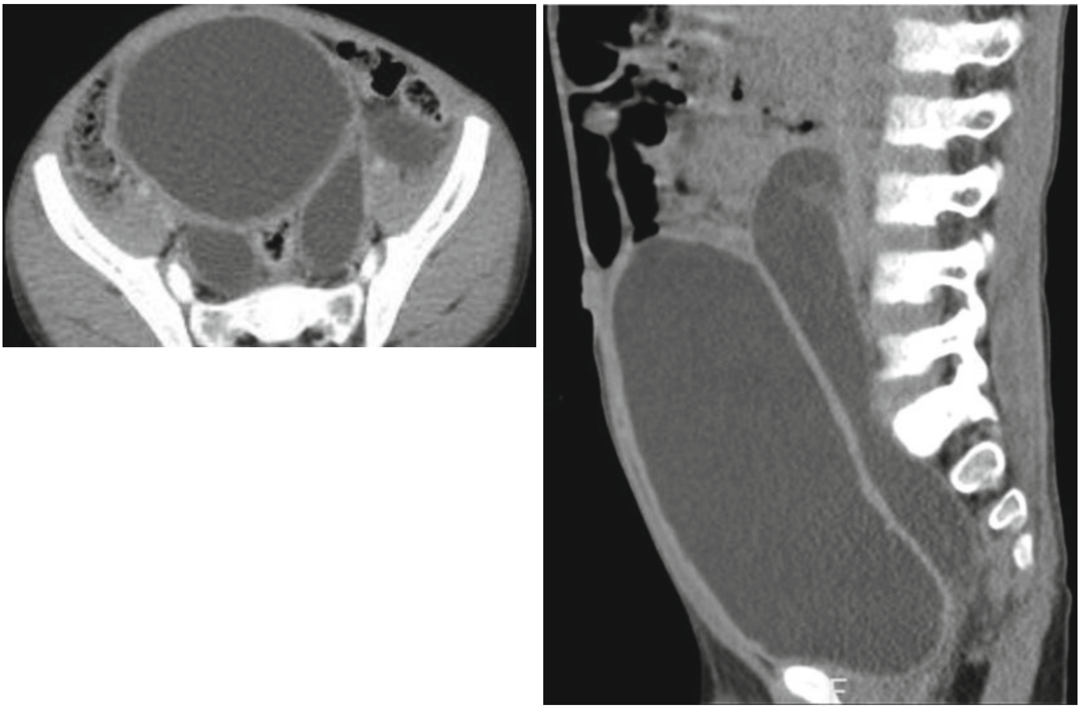
Figs. 1.67, 1.68, and 1.69 Abdominal CT-scan, micturating cystourethrogram and a clinical intraoperative photograph showing megacystis in a patient with microcolon hypoperistalisis syndrome

Congenital Abnormalities of the Bladder

- Bladder exstrophy
- Persistent urachus
- Contracture of the bladder neck
- Bladder diverticulum
- Bladder ears
- Bladder agenesis
- Megacystis
- Bladder duplication
- Bladder septation

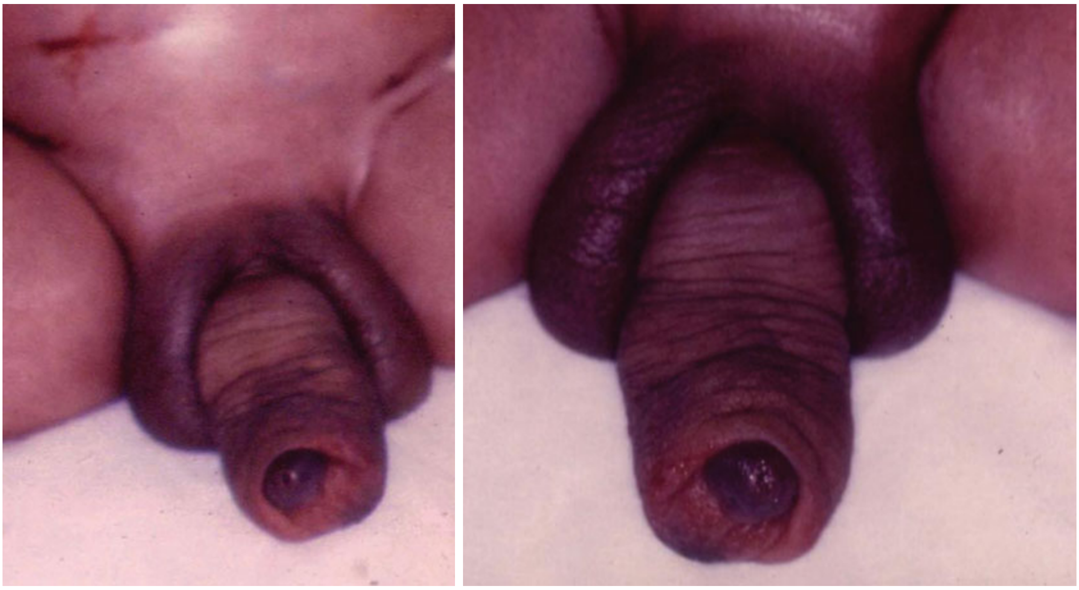
1.6 Abnormalities of the Penis and Urethra in Males

- Apenia:
  - Apenia is a congenital absence of the penis
  - It is extremely rare.
  - More than 50% of patients have associated genitourinary anomalies such as cryptorchidism, renal agenesis and dysplasia.
- Diphallia:
  - Diphallia, penile duplication (PD), diphallic terata, or diphallaspartus is a rare developmental abnormality.



Figs. 1.70 and 1.71 Abdominal CT-scan showing megacystis in a patient with duplex system and hydroureteronephrosis

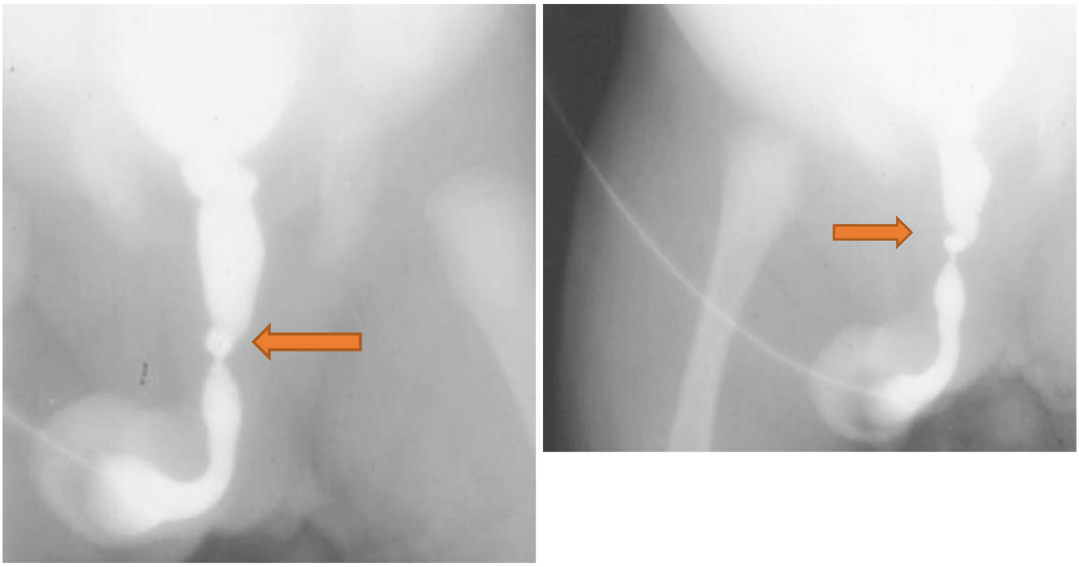
  - It is extremely rare with an estimated incidence of 1 in 5.5 million boys,
  - The first reported case was by Johannes Jacob Wecker in 1609.
  - It is characterized by a male infant with two penises.
  - Infants born with penile diphallia usually are accompanied by renal, vertebral, hindgut, anorectal or other congenital anomalies.
  - There is also a higher risk of spina bifida.
  - Duplication of the penis, or diphallia, is a rare anomaly resulting from incomplete fusion of the genital tubercle.
  - There are two distinct forms of penile duplications:
    - The most common form is associated with bladder-exstrophy complex.
      - The patient exhibits a bifid penis, which consists of two separated corpora cavernosa that are associated with two separate hemiglans.
    - The second form is a true diphallia
      - This is an extremely rare congenital condition.
      - There are several variations of this, ranging from duplication of the glans alone to duplication of the entire lower genitourinary tract.
      - The urethral opening can be in normal position or in a hypospadiac or epispadiac position.
- Megalopenis (Figs. 1.72 and 1.73):
  - Megalopenis is an abnormally enlarged penis.
  - It is seen in children with high level of testosterone production.
  - It is seen also in patients with congenital adrenal hyperplasia.
- Micropenis:
  - Micopenis is defined as an abnormally small but otherwise normally formed penis.
  - The stretched length of the penis is less than 2.5 standard deviation below the mean.



Figs. 1.72 and 1.73 Clinical photographs showing megalopenis

- It is important to distinguish miscropenis from buried and webbed penis, which is usually of normal size.
- The most common causes of micropenis are:
  - Hypogonadotropic hypogonadism
    - Impaired secretion of gonadotrophin-releasing hormone (GnRH) by the hypothalamus occurs in some hypothalamic dysfunctions such as Kallmann's syndrome and Prader-Willi syndrome.
  - Hypergonadotropic hypogonadism
    - The testes are functionally impaired as in gonadal dysgenesis.
  - Idiopathic micropenis
    - There is normal hypothalamic-pituitary-testicular endocrine function.

- Congenital urethral stricture (Figs. 1.74 and 1.75):
  - This is a rare congenital malformation.
  - The two most common sites for congenital urethral stricture are:
    - The fossa navicularis
    - The membranous urethra
  - The effect depends on the severity of the stricture.
  - Severe strictures can affect the bladder and also lead to hydroureter and hydronephrosis which can damage the kidney from back pressure of urine.
- Posterior urethral valves (Figs. 1.76 and 1.77):
  - This is a relatively common congenital malformation,
  - It is seen in male neonates and infants.
  - Posterior urethral valves are found at the distal prostatic urethra.
  - They look like thin membranes and cause varying degrees of obstruction with back-pressure effect on the bladder, ureters and kidneys.
- Hypospadias (Figs. 1.78, 1.79, 1.80, 1.81, and 1.82):
  - This is one of the common urological malformations in males.
  - It occurs in around 1 in 250–300 male births.
  - The urethral meatus is found on the ventral surface of the penis.
  - Around 7 % of patients have an additional family member with hypospadias.



Figs. 1.74 and 1.75 Micturating cystourethrograms showing congenital urethral stricture

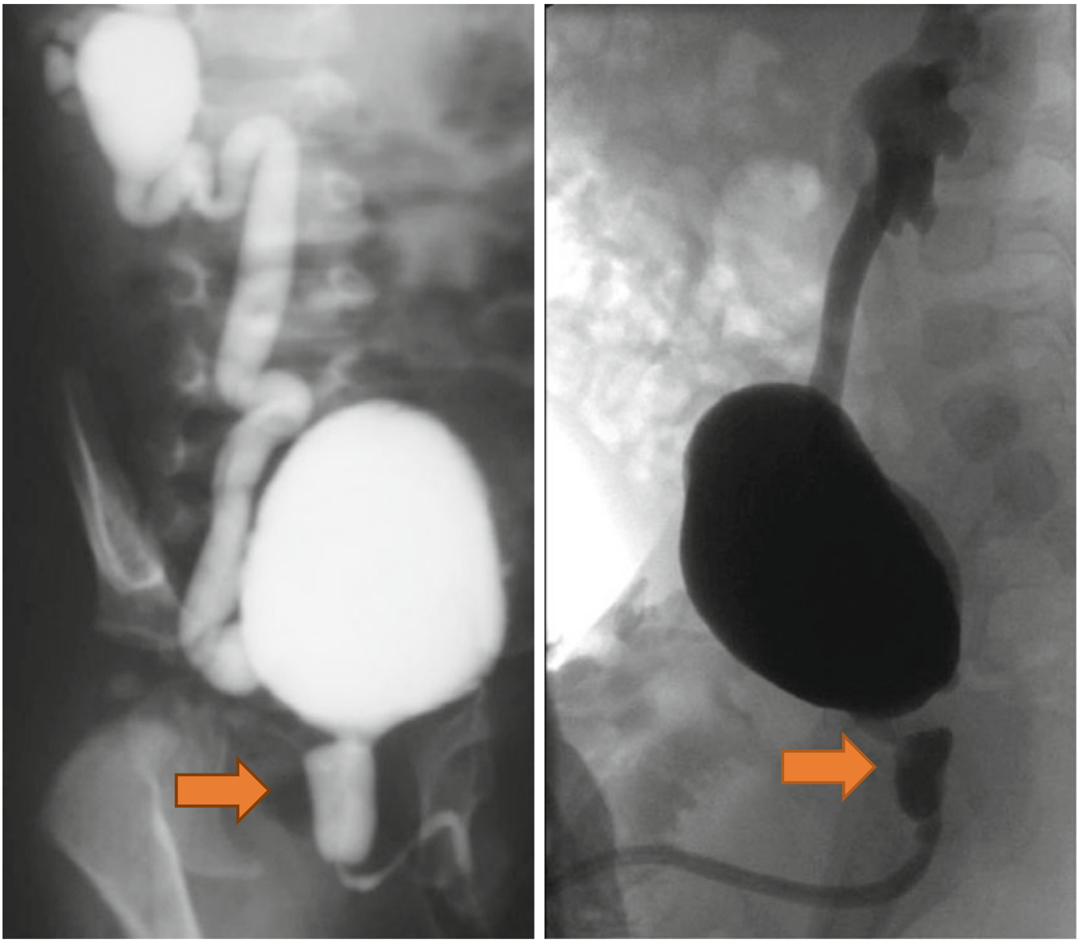
  - Hypospadias is classified based on the site of the abnormal urethral meatus into:
    - Glanular
    - Coronal
    - Subcoronal
    - Distal penile
    - Midpenile
    - Proximal penile
    - Penoscrotal
    - Perineal
  - The site of the abnormal urethral meatus is variable but most cases occur on the distal penis or corona.
  - Around 10 % of children with hypospadias also have cryptorchidism.
  - 9–15 % of cases also have an open processus vaginalis or inguinal hernia.
- Epispadias (Figs. 1.83, 1.84, 1.85, 1.86, 1.87, and 1.88):
  - Epispadias is a relatively rare congenital malformation.
  - It affects males more than females.
  - Epispadias occurs in 1 in 120,000 males and 1 in 450,000 females.
  - In epispadias, the urethral opening is abnormally located on the dorsal aspect of the penis.
  - The extent of the defect can vary from a mild glandular defect to complete defects, as those observed in bladder exstrophy and/or diastasis of the pubic bones.
  - Females with epispadias have a bifid clitoris and separation of the labia.
  - Incontinence is a common problem in those with severe epispadias.

Congenital Abnormalities of the Male External Genitalia and Urethra

- Apenia
- Diphallia
- Megalopenis
- Micropenis
- Congenital urethral stricture
- Posterior urethral valves
- Hypospadias
- Epispadias

1.7 Abnormalities of Female External Genitalia

- Distal urethral stenosis:
  - This occurs in young girls with enuresis with slow and interrupted stream and recurrent infection.



Figs. 1.76 and 1.77 Micturating cystourethrogramms showing posterior urethral valve. Note the dilated posterior urethra. Note also the associated unilateral VUR

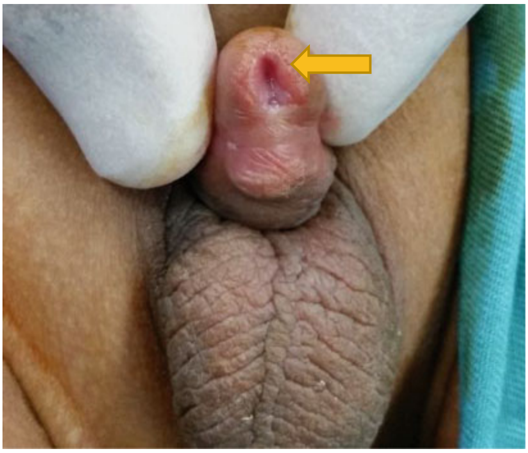
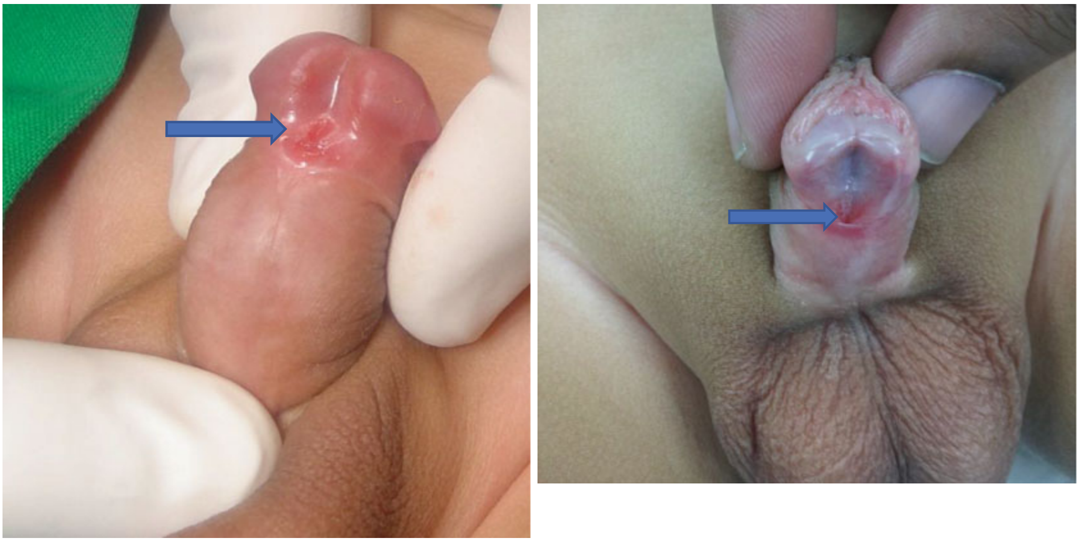
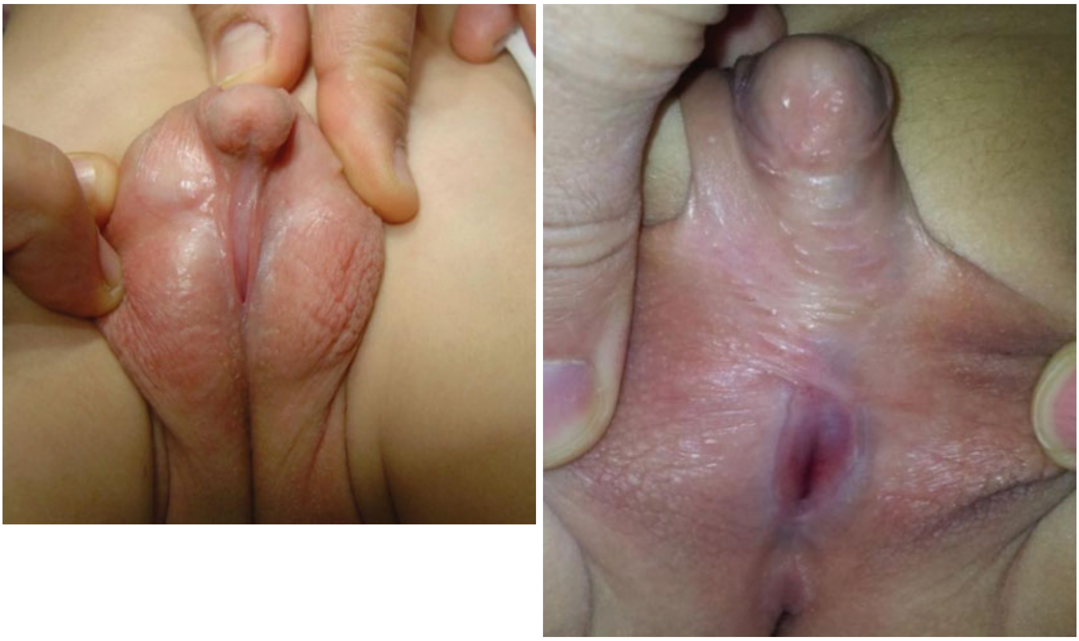


Fig. 1.78 A clinical photograph showing hypospadias. Note the site of urethral opening which is located more proximally

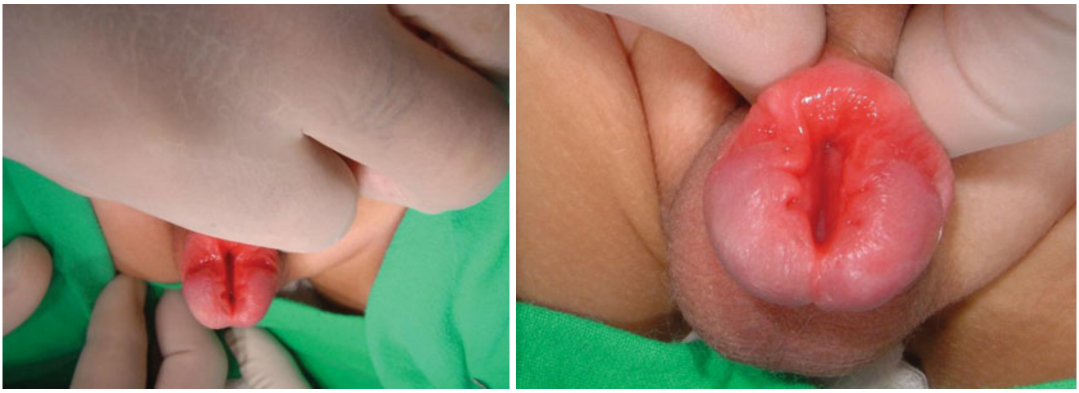
  - It is associated with secondary spasm of the external sphincter.
- Labial fusion:
  - Fused labia minora are relatively common.
  - The two labia minora are fused together.
  - They can cause recurrent urinary infection as a result of obstruction to the urine flow.
  - Treatment is simple by separating the two labia minor
  - The use of estrogen cream can be prevent recurrence which is common in these patients.
- Female epispadias:
  - Female epispadias is extremely rare.



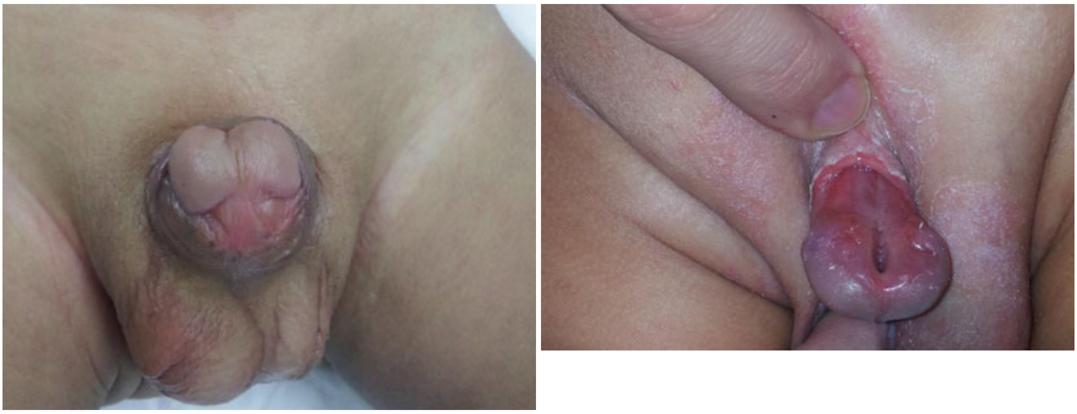
Figs. 1.79 and 1.80 Clinical photographs showing distal and mid penile hypospadias



Figs. 1.81 and 1.82 Clinical photographs showing severe degrees of hypospadias (Penoscrotal and perineal hypospadias)



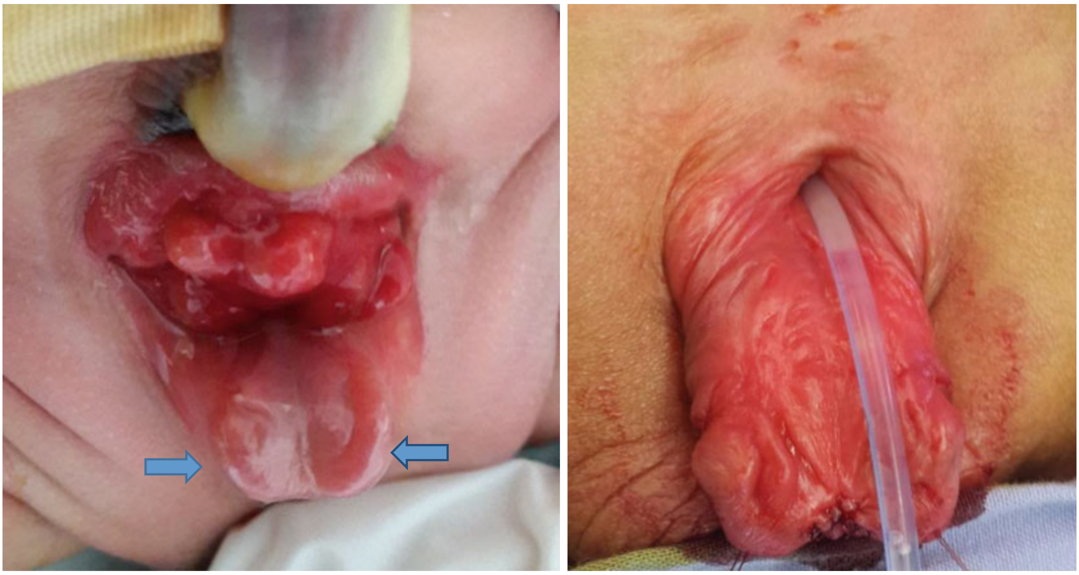
Figs. 1.83 and 1.84 Clinical photographs showing glanular epispadias. Note the urethral opening on the dorsum of the glans. This is considered a rare variant of epispadias. This type has an excellent prognosis as the urethral sphincter is normal in these patients



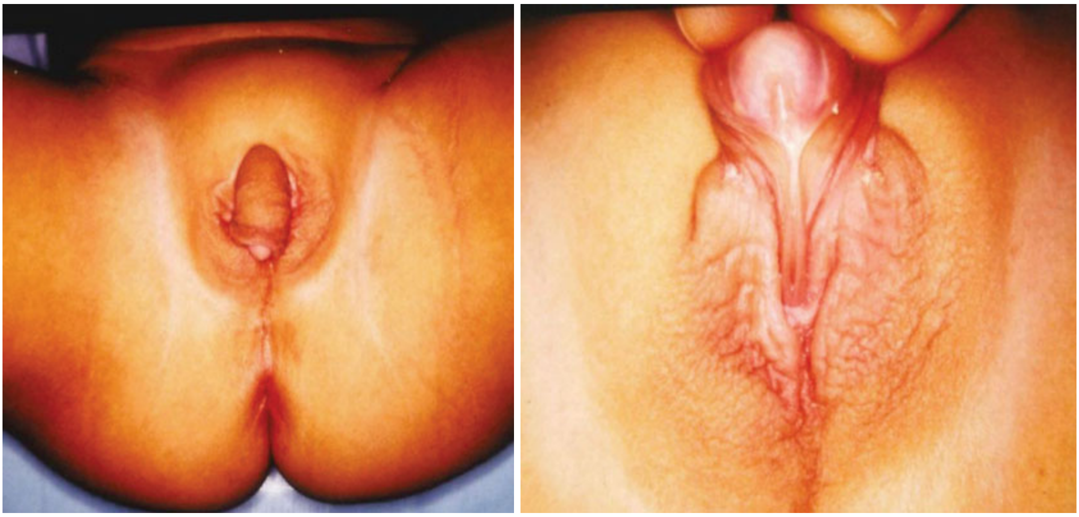
Figs. 1.85 and 1.86 Clinical photographs showing complete epispadias that is not associated with bladder exstrophy. Note the extent of the epispadias opening and note also the associated dorsal curvature of the penis

- The reported incidence is approximately 1 of 500,000–600,000 live girls.
- Epispadias in females is commonly associated with separated pubic bones.
- Female epispadias is characterized by:
  - A bifid clitoris.
  - Diastases of the corpora cavernosa.
  - Flattening of the mons.
  - Separation of the labia.
- The diagnosis of epispadias in females is always delayed as the defect may not be obvious.
- The bladder neck is almost always involved in these patients leading to urinary incontinence.
- Repair of female epispadias is much simpler.
- The two parts of the clitoris are sutured together and the urethra is positioned in its normal place.
- The prognosis of these patients is good and fertility is not affected.

- Clitoral hypertrophy (Figs. 1.89, 1.90, and 1.91):
  - Clitoromegaly (or macroclitoris) is an abnormal enlargement of the clitoris.
  - It is also called clitoromegaly.
  - It is commonly congenital but can be acquired following the use of anabolic steroids, including testosterone.
  - Clitoromegaly is commonly caused by fetal exposure to androgens as seen in those with congenital adrenal hyperplasia.



Figs. 1.87 and 1.88 Clinical photographs showing epispadias as part of the epispadias-exstrophy complex. In the first photograph, the bladder exstrophy is still not repaired while in the second one bladder exstrophy closure was already done. The size of the phallus was increased by long acting testosterone



Figs. 1.89 and 1.90 Clinical photographs showing clitromegaly in a patient with congenital adrenal hyperplasia

  - Rarely, it may also be due to in utero exposure to progestational agents or idiopathic virilisation.
  - Clitoromegaly should not be confused with dermoid cyst of the clitoris.
- Urethral prolapse:
  - Urethral prolapse is a circular protrusion of the distal urethra through the external meatus.
  - It is a rarely diagnosed in female children and commonly occurs in prepubertal females and postmenopausal women.
  - Extremely rare, the urethral prolapse can become strangulated.
  - Vaginal bleeding is the most common presenting symptom of urethral prolapse.

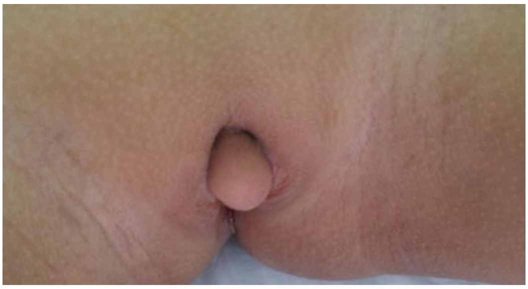


Fig. 1.91 A clinical photogram showing dermoid cyst of the clitoris which can be confused with cliteromegaly

- Clinically, a round doughnut-shaped mucosa is seen protruding from the urethral opening.
- Management of urethral prolapse ranges from medical therapy that consists of topical estrogen use to conservative surgical excision when medical therapies fail.

Congenital Abnormalities of the Female External Genitalia and Urethra

- Distal urethral stenosis
- Labial fusion
- Clitoral hypertrophy
- Urethral prolapse

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Hydronephrosis in Infants and Children

2

2.1 Introduction

- The word “hydro” represents “water” and “nephro” represents “kidney”.
- Hydronephrosis means “water inside the kidney”.
- Hydronephrosis is defined as distension and dilation of the renal pelvis and calyces (Figs. 2.1 and 2.2).
- Hydroureteronephrosis refers to distention of both the ureter and the renal pelvis and calices.
- Hydronephrosis is usually caused by obstruction of the free flow of urine from the kidney.
- Hydroureteronephrosis is usually caused by obstruction at the uretrovesical junction or below.
- The signs and symptoms of hydronephrosis depend upon:
  - Whether the obstruction is acute or chronic
  - Whether the obstruction is partial or complete
  - Whether the obstruction is unilateral or bilateral
  - Hydronephrosis that occurs acutely with sudden onset can cause intense pain in the flanks (Dietl’s crisis).
- If symptoms occur they can include:
  - Back, flank or lower abdominal pain
  - Nausea and vomiting
  - Dysuria
  - Burning during micturition
  - Urinary incontinence
  - Hematuria
  - Febrile urinary tract infections
- Hydronephrosis should be graded accurately in order to make good clinical decisions concerning the management and follow-up.
- There are currently two methods to grade the degree of hydronephrosis:
  - The simple classification system of “mild, moderate, and severe” is less accurate.
  - The Society for Fetal Urology (SFU) has developed a more accurate numerical grading system for hydronephrosis.
- The causes of hydronephrosis can be congenital or acquired.
- It is important to understand that hydronephrosis does not always mean there is obstruction to the flow of urine from the kidney and hydronephrosis is a secondary effect of some other disease. Thus, the terms hydronephrosis and obstruction should not be used interchangeably.
- With the widespread use of prenatal ultrasounds, antenatal hydronephrosis is currently the most common diagnosed prenatal condition.
- Hydronephrosis can be caused by obstruction anywhere along the upper or lower urinary tract.
  - Obstruction that occurs anywhere along the upper urinary tract will lead to increased pressure within the kidney.
  - Obstruction occurring in the lower urinary tract can also cause this increased pressure through efflux of urine into the kidney.

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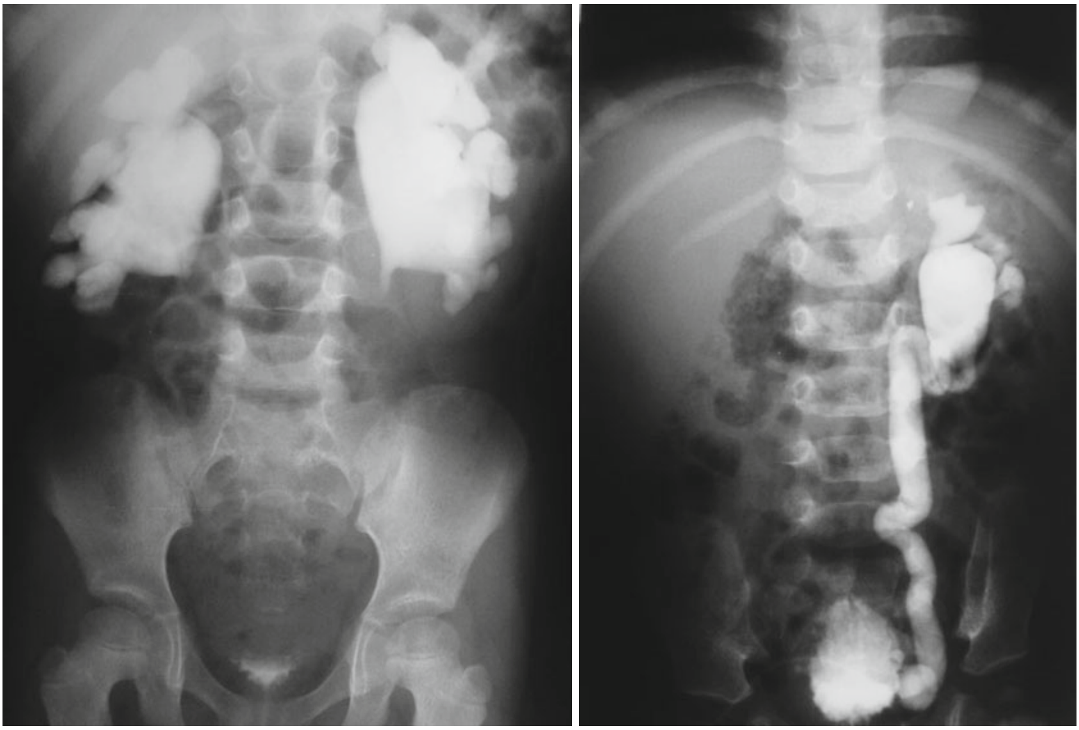
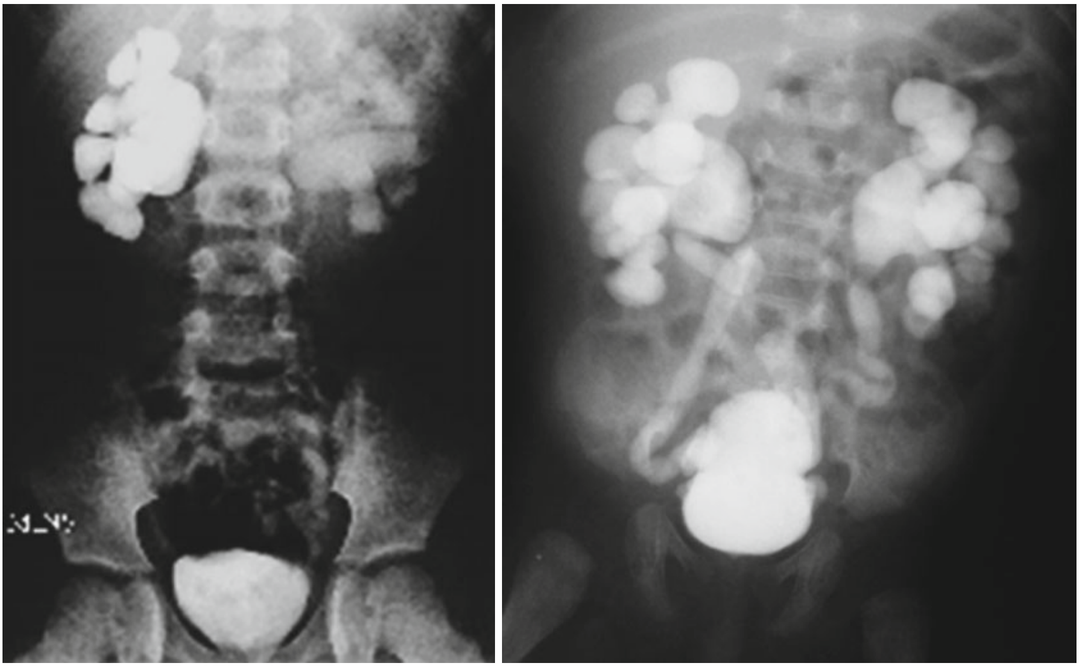
A.H. Al-Salem, *An Illustrated Guide to Pediatric Urology*, DOI 10.1007/978-3-319-44182-5_2



Figs. 2.1 and 2.2 Intravenous urogram and a micturating cystourethrogram showing bilateral hydronephrosis and unilateral hydroureteronephrosis

  - This would eventually lead to:
    - Urinary tract infection
    - Stone formation
    - Loss of renal function
- Neonatal hydronephrosis can be caused by several abnormalities. These commonly include (Figs. 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, and 2.9):
  - Ureteropelvic junction obstruction
  - Vesicoureteral reflux
  - Ureterovesical junction obstruction
  - Megaureter
  - Ureterovesical junction obstruction and megaureter are fairly uncommon and, therefore, pediatric patients who have hydronephrosis and a normal voiding cystourethrogram are presumed to have ureteropelvic junction obstruction.
- Prenatally diagnosed hydronephrosis:
  - Approximately 50 % are transient and resolve by the time the infant is born.
  - In 15 %, the hydronephrosis persists (nonrefluxing, non-obstructing hydronephrosis) but spontaneously regress by age 3 years.
  - In the remaining 35 %, a pathological cause can be identified.
- Extensive use of prenatal ultrasound has led to an increased rate of diagnosis of neonatal hydronephrosis, of which ureteropelvic junction obstruction is the most frequent cause.
- Ureteropelvic junction obstruction occurs in approximately 1 in every 2,000 live births and accounts for approximately half of the cases of prenatal hydronephrosis.
- In most cases, neonatal hydronephrosis secondary to ureteropelvic junction obstruction gradually resolves without surgical intervention.
- There is a strong correlation between the Society for Fetal Urology (SFU) grade of hydronephrosis and the likelihood of spontaneous resolution:
  - Grade I resolves in approximately 50 % of patients

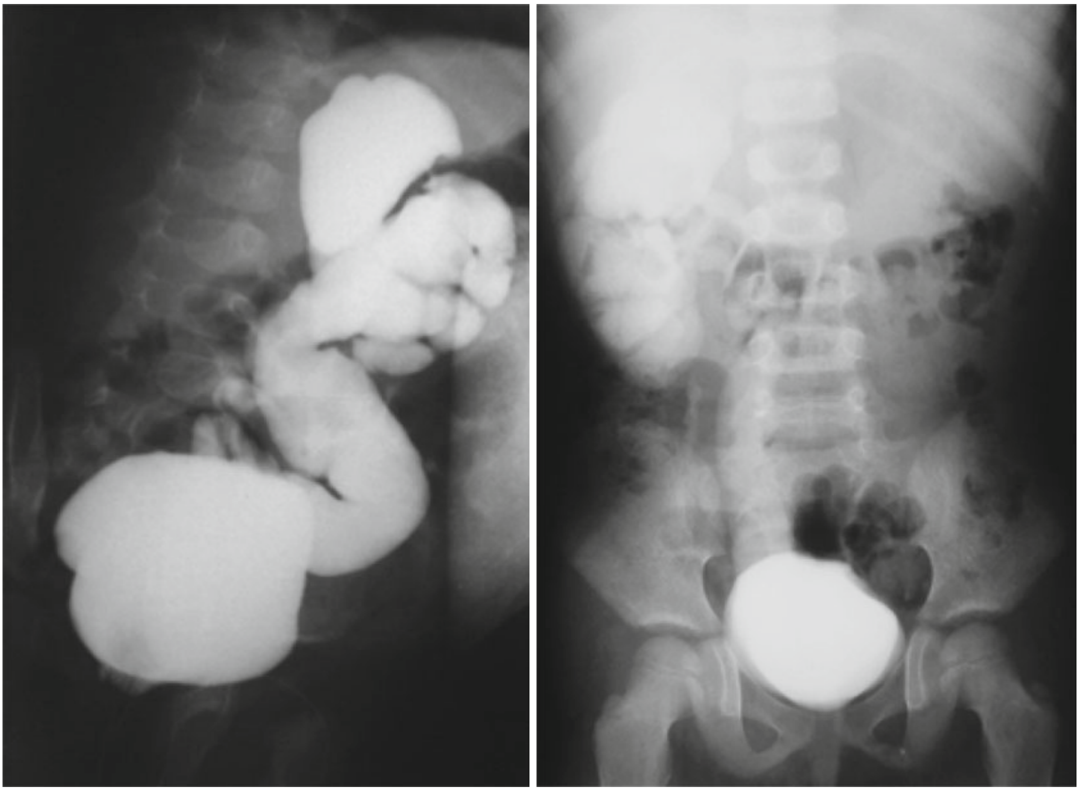


Figs. 2.3 and 2.4 Intravenous urography and micturating cystourethrogram showing pelviureteric junction obstruction and bilateral vesicoureteric reflux

  - Grades II resolves in approximately 36 % of patients
  - Grade III resolves in approximately 16 % of patients
  - Grade IV resolves in approximately 3 % of patients
- The initial severity of the hydronephrosis at the time of antenatal diagnosis and the presence of the hydronephrosis at birth were the only two factors that predicted hydronephrosis failure to resolve.
- Hydronephrosis that was mild to mild-to-moderate in severity resolved in 71 % of patients, compared to 28 % of children with moderate to severe hydronephrosis. This supports the claim that the severity of hydronephrosis predicts failure of the lesion to resolve.

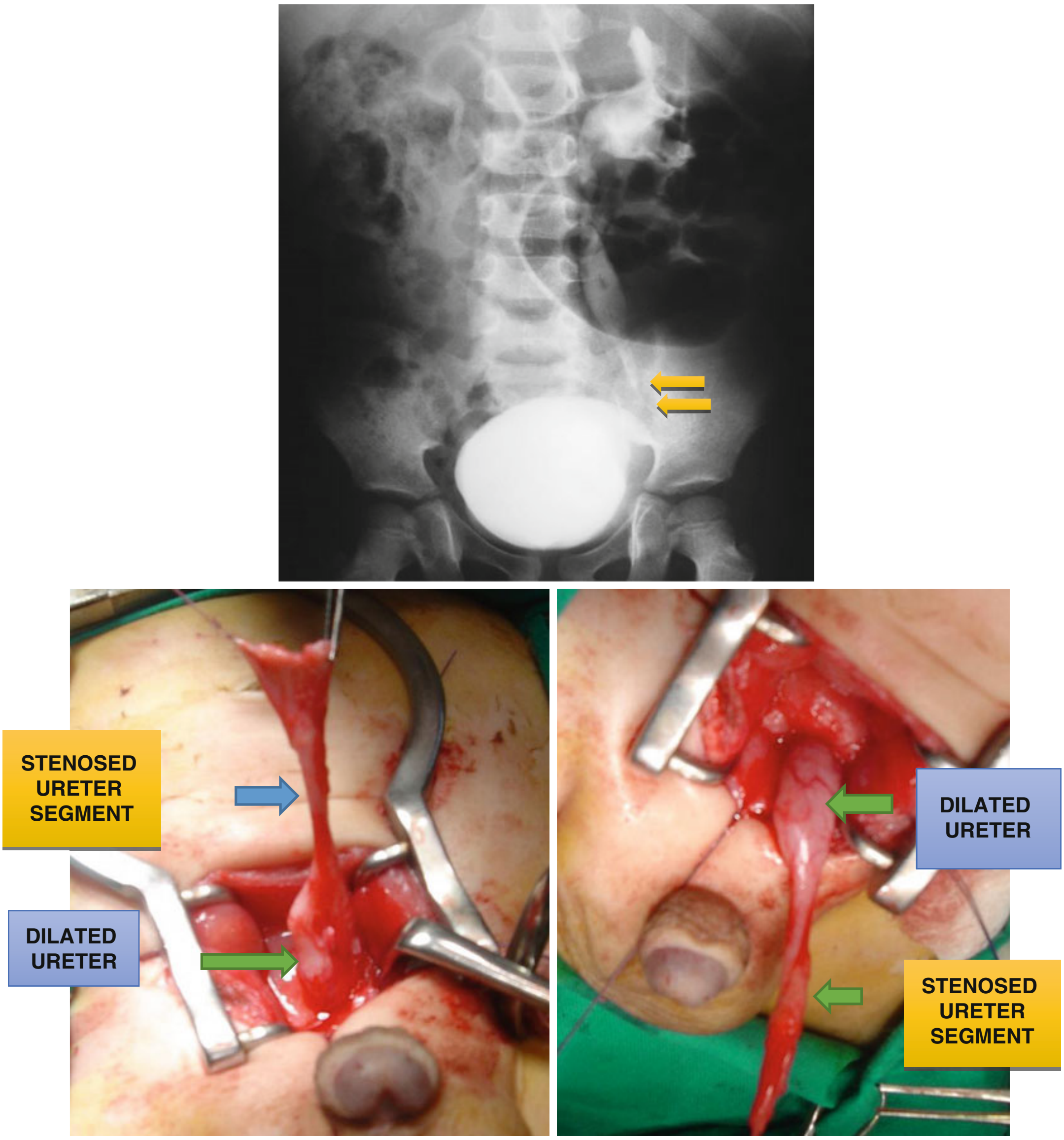
2.2 Pathophysiology

- Hydronephrosis can result from anatomic or functional causes that interrupt the flow of urine (Figs. 2.10 and 2.11).
- This interruption can occur anywhere along the urinary tract from the kidneys to the urethral meatus.
- Gross changes within the urinary tract depend on:
  - The duration of obstruction
  - The degree of obstruction
  - The level of obstruction
- Within the intrarenal collecting system, the degree of dilation is limited by surrounding renal parenchyma.
- This is in contrast to the extrarenal components which can dilate to the point of tortuosity.
- Hydronephrosis can reasonably be viewed as a beneficial compensatory mechanism that actually protects the kidney against high intrapelvic pressures and further renal damage.
- The extent and persistence of these functional insults are directly related to the duration and severity of the obstruction.
  - Brief disruptions lead to reversible functional disturbances with little associated anatomic changes.



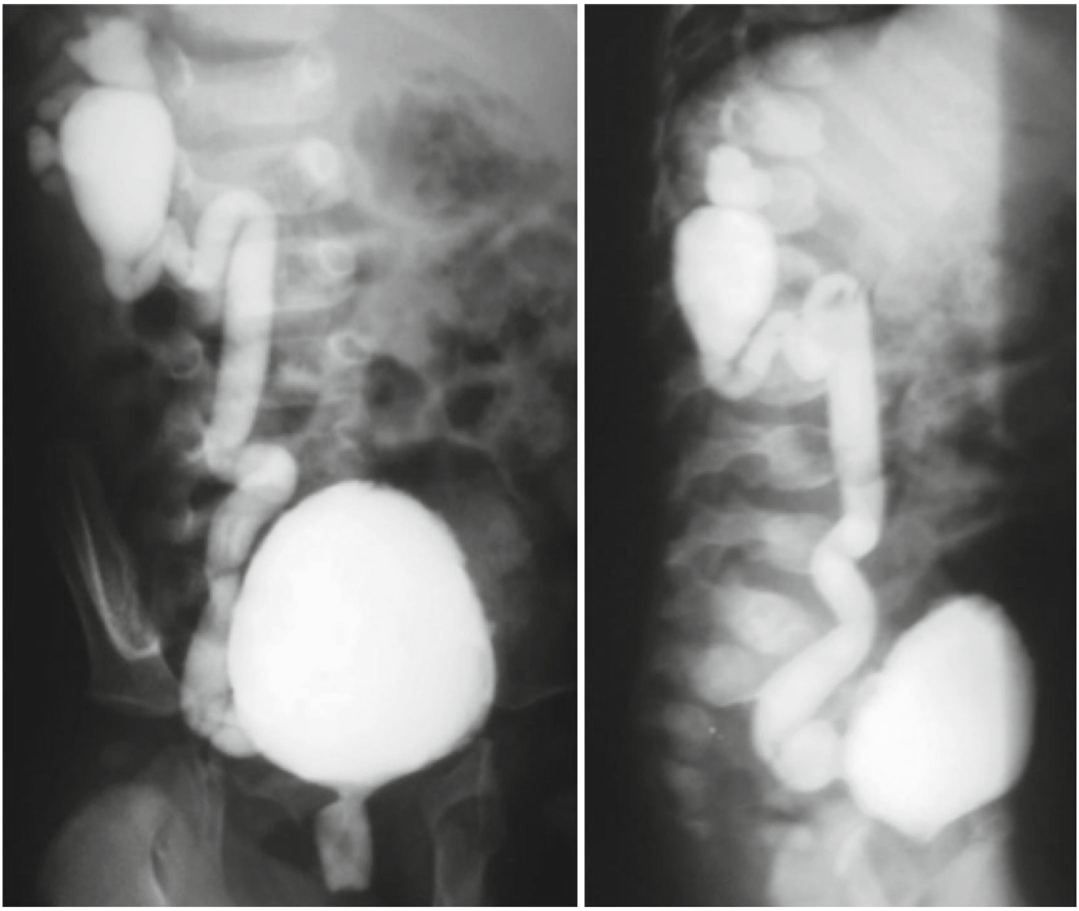
Figs. 2.5 and 2.6 A micturating cystourethrogrma showing severe vesicoureteric reflux in a patient with a duplex system. An intravenous urogram showing a negaureter with hydroureteronephrosis is seen in the second picture. In patients with megaureter, there is no anatomical obstruction at the uretrovesical junction and micturating cystourethrogram doe not show vesico ureteric reflux

  - More chronic disruptions lead to profound tubular atrophy and permanent nephron loss.
- The rise in ureteral or renal pelvic pressure leads to marked changes in glomerular filtration, tubular function, and renal blood flow.
- The glomerular filtration rate (GFR) declines significantly within hours following acute obstruction. This significant decline of GFR can persist for weeks after relief of obstruction.
- In addition, renal tubular ability to transport sodium, potassium, to concentrate and to dilute the urine is severely impaired.
- Increased ureteral pressure also results in pyelovenous and pyelolymphatic backflow.
- Acute hydronephrosis:
  - Acute hydronephrosis when corrected, usually allows full recovery of renal function.
  - It can be associated with little anatomic disturbance to renal parenchyma.
- Chronic hydronephrosis:
  - In chronic hydronephrosis, the loss of function is usually irreversible even with correction of the obstruction.
  - It may be associated with compression of the papillae, thinning of the renal parenchyma around the calyces, and coalescence of the septa between calyces.
  - Eventually, cortical atrophy progresses to the point at which only a thin rim of parenchyma is present (Figs. 2.12, 2.13, and 2.14).
  - Microscopic changes consist of dilation of the tubular lumen and flattening of the tubular epithelium. Fibrotic changes and increased collagen deposition are observed in the peritubular interstitial tissue.



Figs. 2.7, 2.8, and 2.9 An intravenous urogram showing hydrouretronephrosis secondary to obstruction at the uretrovesical junction. Note the ureter tapering at the lower part. This was confirmed intraoperatively in the second two intraoperative picrures. Note the dilated ureter above the site of obstruction. This was treated by resection of the stenotic part and reimplantation of the ureter

  - Long-standing hydronephrosis may be associated with obstructive nephropathy and renal failure.
  - Patients with complete or severe partial bilateral obstruction also may develop acute or chronic renal failure.
- Urinary stasis as a result of obstruction may be complicated by:
  - Infection
  - Renal scarring
  - Calculus formation
  - Sepsis
- Hypertension is occasionally induced by renal obstruction.
- The mechanism responsible for the elevation in blood pressure varies with the duration and type of obstruction.



Figs. 2.10 and 2.11 Two micturating cystourethrograms showing hydrouretronephrosis with dilated urinary bladder secondary to posterior urethral valve. Note the tortuous dilated ureter

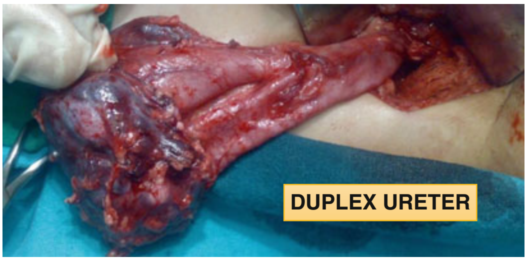


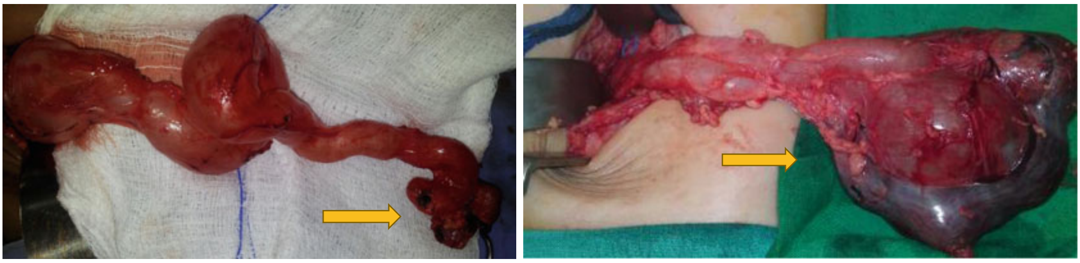
Fig. 2.12 Intraoperative photograph showing an atrophic kidney with dilated refluxing duplex system. Note the markedly dilated duplex ureter

  - Acute, unilateral obstruction can cause hypertension via activation of the renin-angiotensin system.
  - The elevation in blood pressure is probably volume mediated as renin secretion is usually normal in patients with bilateral urinary tract obstruction or obstruction of a solitary functioning kidney. The elevation in blood pressure resolves with the diuresis following correction of the obstruction.
  - The plasma renin activity is also typically normal in chronic unilateral obstruction, and the elevation in blood pressure is unrelated to the renal disease.
- The pathophysiological changes of hydronephrosis depends on several factors which can be summarized as follows:
  - Persistent hydronephrosis will lead to the following changes:
    - Dilatation of the renal pelvis and the intrarenal collecting system.
    - The degree of dilatation is limited by surrounding renal parenchyma.

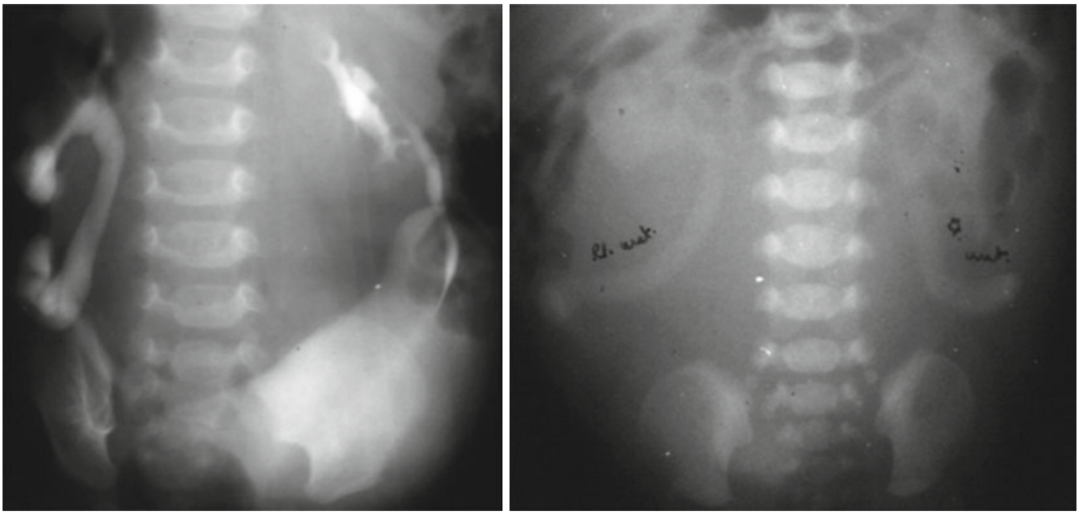
    - This will lead to compression of the papillae, thinning of the parenchyma around the calyces, and coalescence of the septa between calyces.
    - Eventually, cortical atrophy progresses to the point at which only a thin rim of parenchyma is present.
    - Fibrotic changes and increased collagen deposition are also observed in the peritubular interstitium.
    - The extrarenal dilatation can progress leading to ureteral dilatation to the point of tortuosity.
  - Urinary stasis in these patients may result in complications including:
    - Infection
    - Renal scarring
    - Calculus formation
    - Sepsis
    - Loss of renal function
  - Longstanding hydronephrosis may be associated with obstructive nephropathy, hypertension and renal failure.

2.3 Etiology of Hydronephrosis

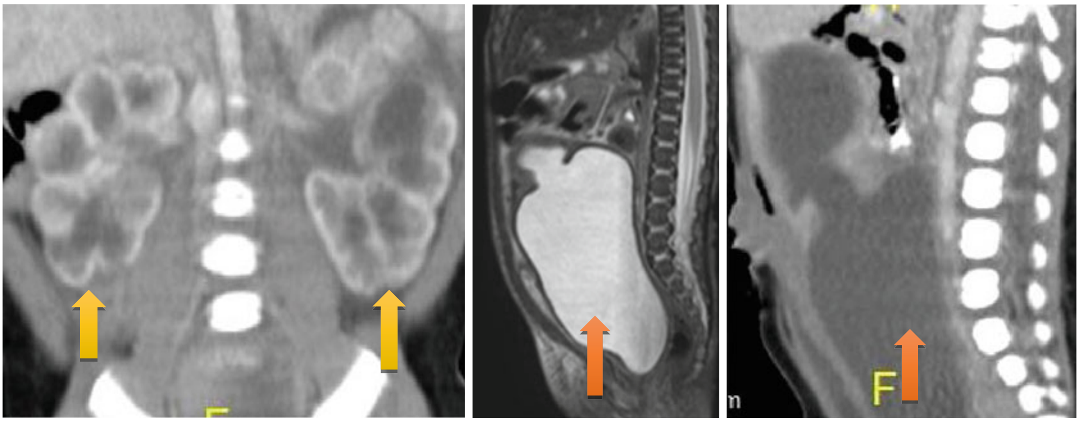
- The etiology and presentation of hydronephrosis and/or hydroureter in adults differ from that in neonates and children (Figs. 2.15, 2.16, 2.17, 2.18, 2.19, 2.20, 2.21, 2.22, 2.23, 2.24, 2.25, 2.26, 2.27, 2.28, 2.29, 2.30, 2.31, 2.32, 2.33, and 2.34).



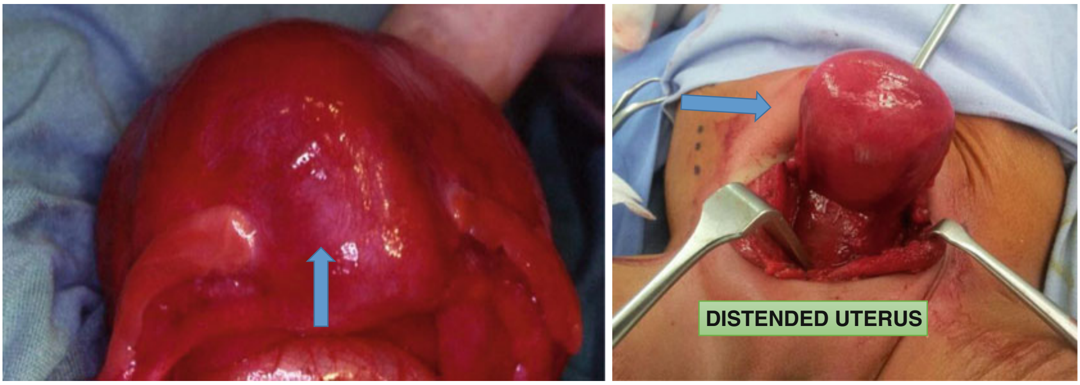
Figs. 2.13 and 2.14 Intraoperative photographs showing atrophic kidneys secondary to severe reflux and hydroureters



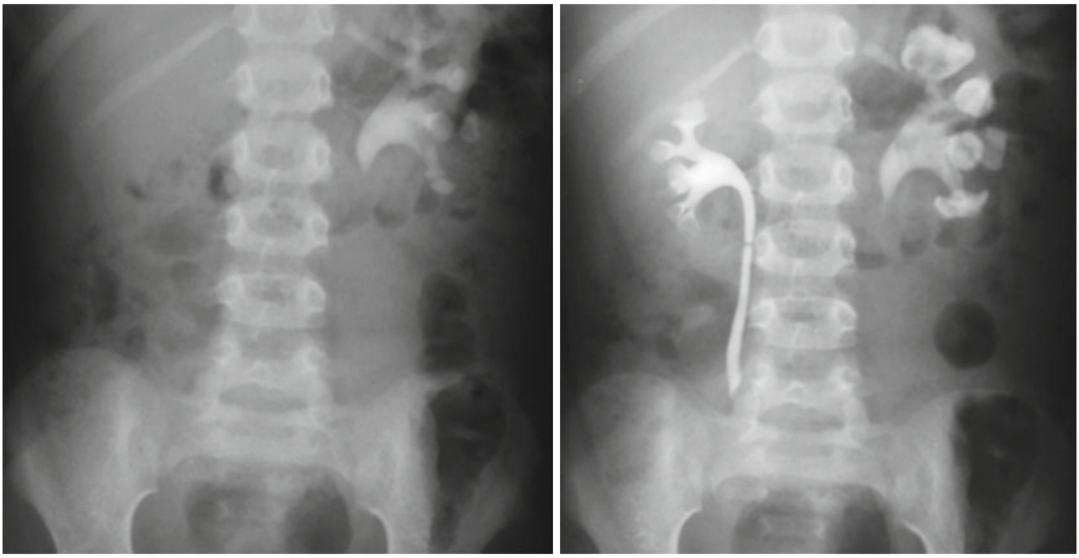
Figs. 2.15 and 2.16 Intravenous urography showing bilateral hydroureters and hydronehrosis secondary to exteral compression by a distended vagina and uterus (hydrometrocolpos) secondary to vaginal atresia. This will resolve once the vaginal atresia is treated



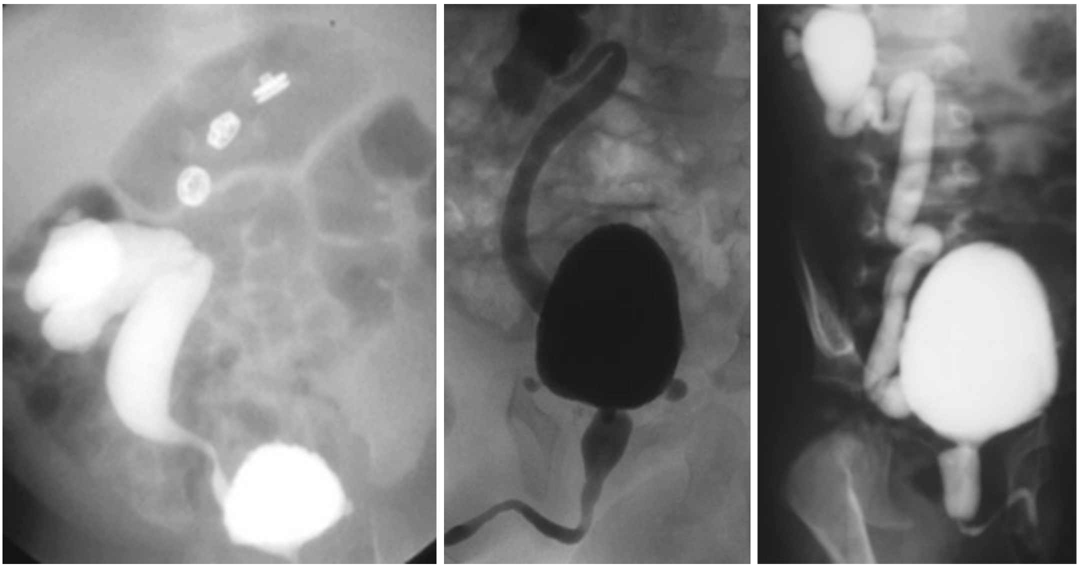
Figs. 2.17, 2.18, and 2.19 MRI showing bilateral hydronephrosis and distended vagina secondary to vaginal atresia



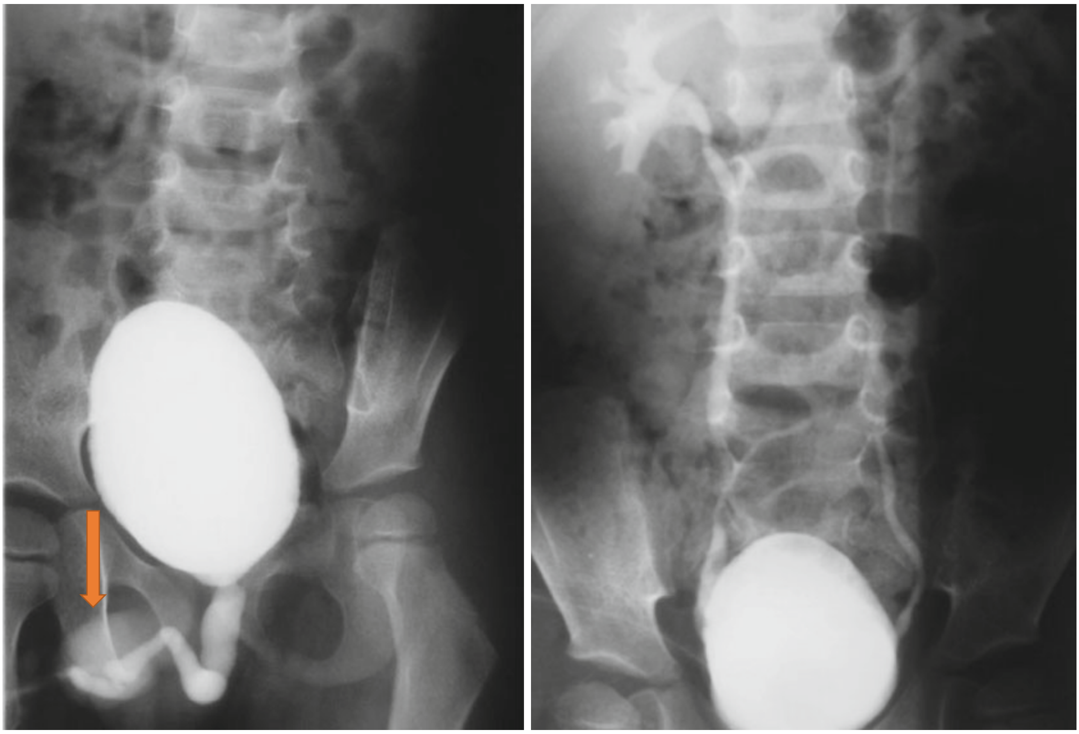
Figs. 2.20 and 2.21 Inra-operative photographs showing hydrometrocolpos secondary to vaginal atresia. The distended vagina and uterus will lead to compression on the ureters leading to hydroureteronephrosis. Drainage of the hydrometrocolpos will lead to relief of the obstruction and resolution of the hydroureteronephrosis



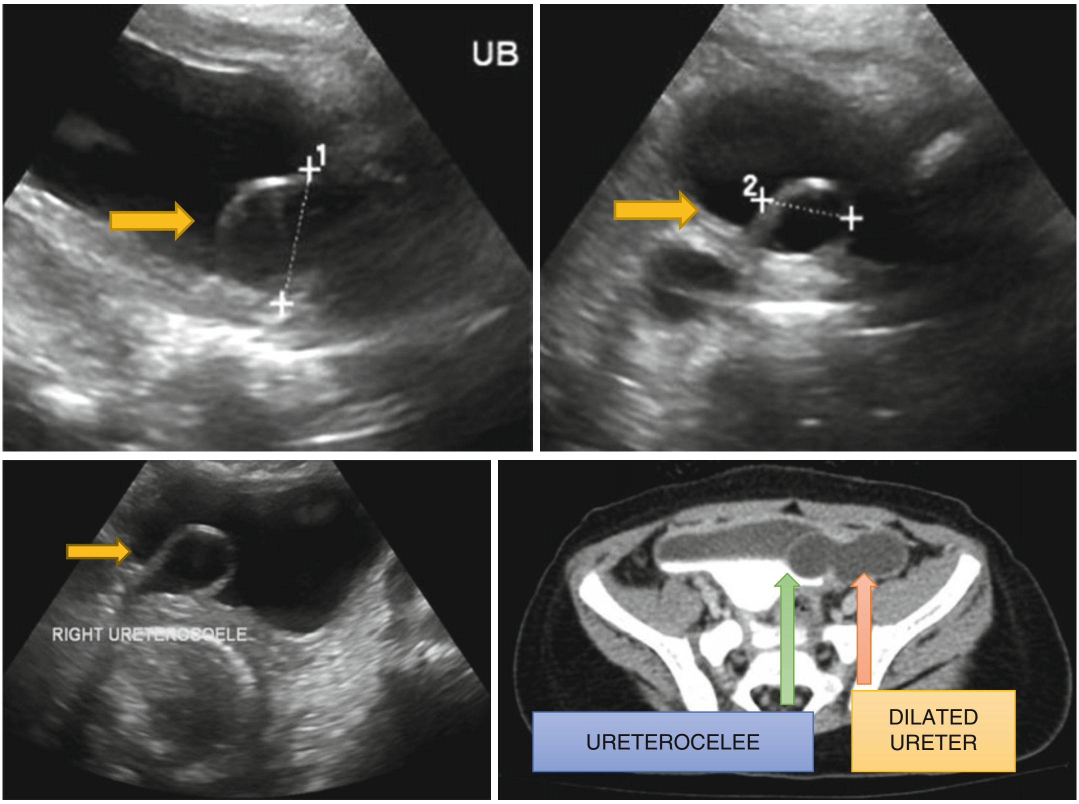
Figs. 2.22 and 2.23 Plain abdominal x-ray and IVU showing a staghorn stone in a child causing hydronephrosis. The stone took the shape of the renal pelvis and cayces. Note the stone is causing obstruction and hydronephrosis on the IVU



Figs. 2.24, 2.25, and 2.26 Intravenous urogram and voiding cystourethrogrms showing unilateral hydroureteronephrosis secondary to uretrovesical obstruction and posterior urethral valve

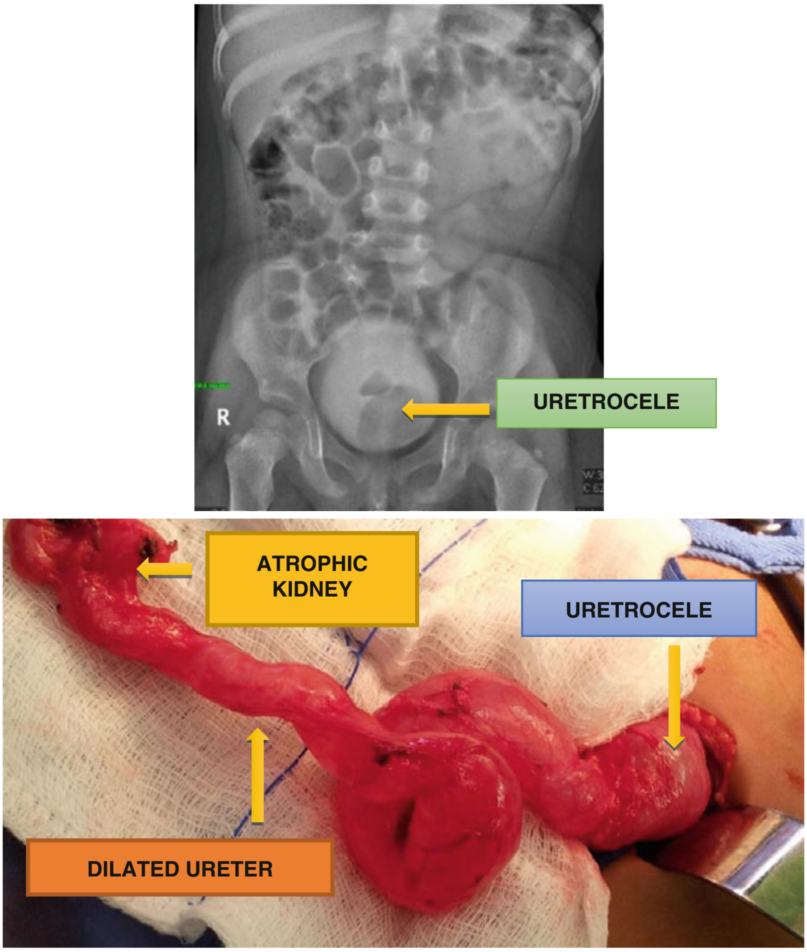


Figs. 2.27 and 2.28 A voiding cystourethrogram showing urethral stricture causing vesicoureteral reflux with hydroureter and hydronephrosis



Figs. 2.29, 2.30, 2.31, and 2.32 Abdominal and pelvic ultrasound and CT-scan showing right and left uretrocele with hydroureter and hydronephrosis

- The causes of hydronephrosis with or without hydroureter depends on:
  - The site of obstruction
  - Whether it is unilateral or bilateral
  - Whether it is intrinsic, extrinsic or functional.
- The following are the main causes of hydronephrosis in infants and children:
  - Pelvi-ureteric junction obstruction
  - Ureterovesical junction obstruction
  - Ureteral folds and valves
  - Benign fibroepithelial polyps
  - Retrocaval ureter
  - Neurogenic bladder
  - Hydrocolpos and hydrometrocolpos
  - Bladder exstrophy
  - Duplicated renal collecting systems
  - Multi cystic dysplastic kidney
  - Retroperitoneal lymphoma and sarcoma
  - Retroperitoneal fibrosis
  - Renal, bladder and ureteric calculi
  - Vesicoureteric reflux
  - Posterior urethral valve
  - Urethral stricture
  - Uretrocele
  - Posterior urethral valves
  - Urethral atresia
  - Phimosis and meatal stenosis
- Multi cystic dysplastic kidney (MCDK) (Figs. 2.35, 2.36, and 2.37):
  - This will show several round, well defined, cystic structures within the kidney that often look just like severe hydronephrosis.
  - These abnormally developed kidneys are generally found early in pregnancy through antenatal ultrasounds.
  - The true diagnosis can be confirmed postnatally by the following tests:



Figs. 2.33 and 2.34 A cystogram showing an uretrocele and intraoperative photograph showing a large ureterocel causing obstruction and marked hydroureter and atrophic dysplastic kidney

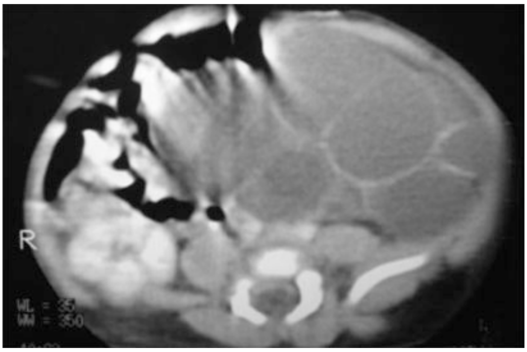
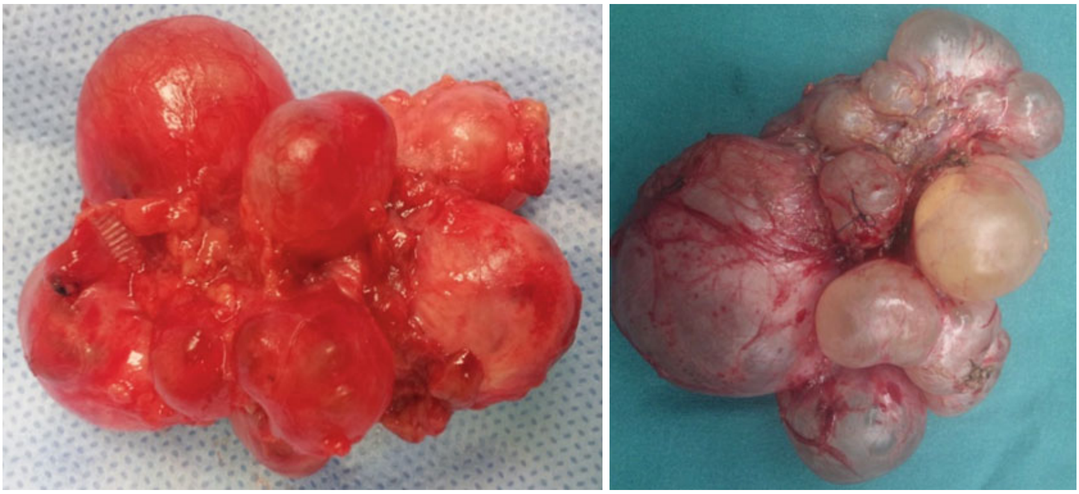
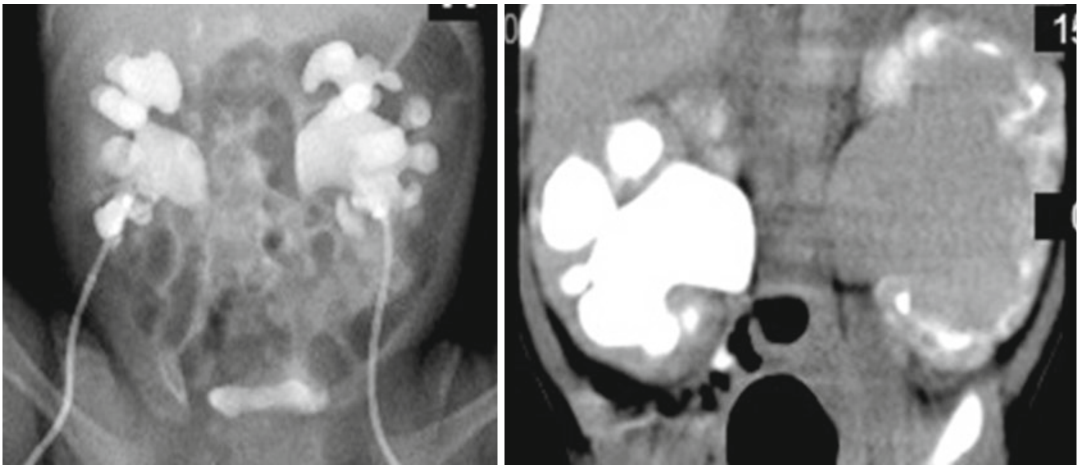


Fig. 2.35 CT-scan showing multicystic dysplastic kidney

  - A post-natal ultrasound
  - A voiding cystourethrogram
  - A nuclear renal scan
- The renal scan confirms that the kidney has no function.
- MCDKs have no function and will involute (shrink up) over time.
- Rarely, these multi cystic dysplastic kidneys needs to be removed for the following reasons:
  - Very large multi cystic dysplastic kidney
  - If they fail to involute
  - If they rupture

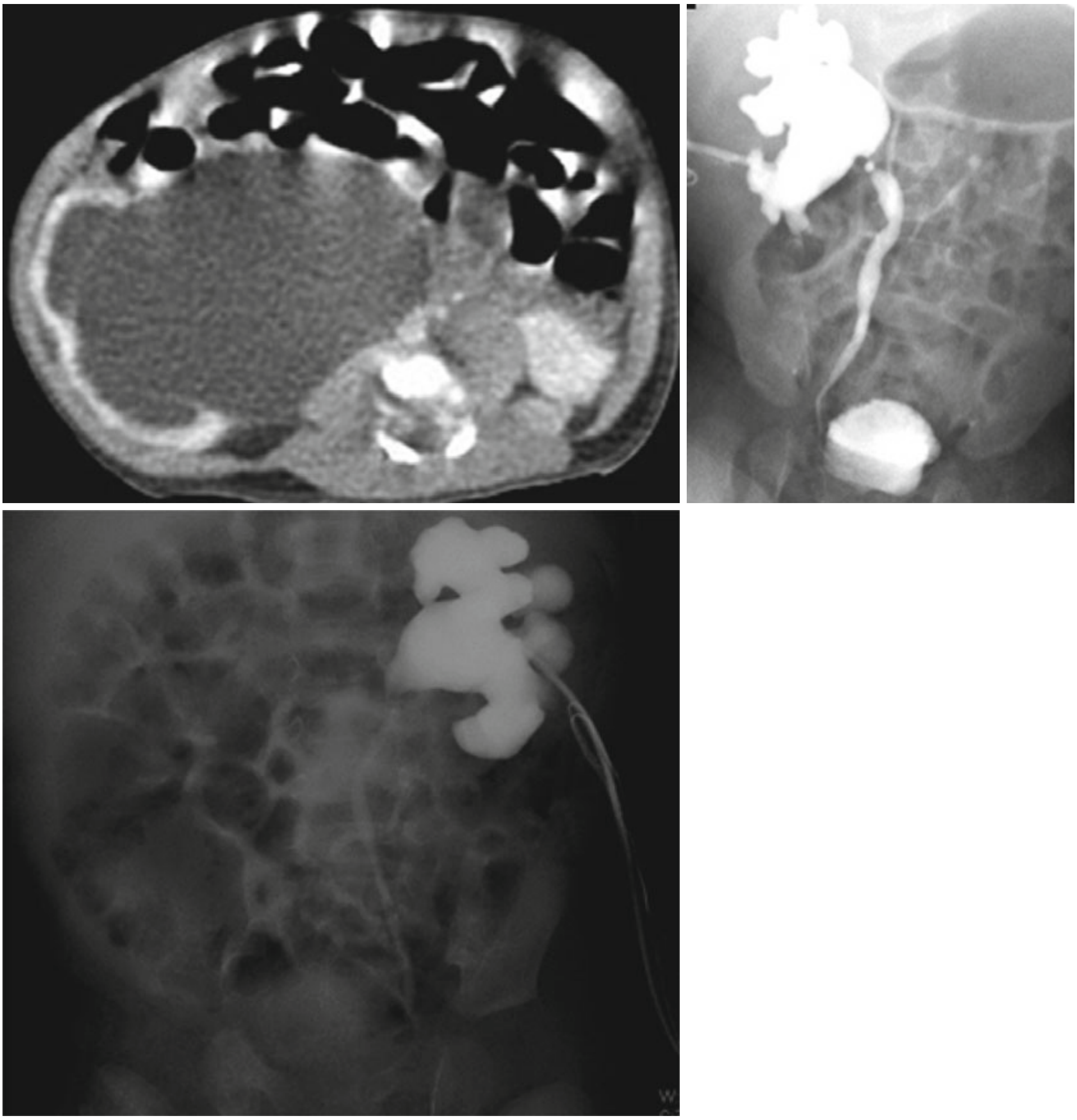


Figs. 2.36 and 2.37 Clinical photographs showing resected multicystic dysplastic kidneys



Figs. 2.38 and 2.39 Bilateral nephrostograms and CT-scan showing bilateral PUJ obstruction

    - If they develop unmanageable high blood pressure
    - If they are complicated by severe infection
- There are several congenital and acquired conditions that can lead to hydronephrosis in infants and children.
- Congenital causes:
  - PUJ (Pelvi-Ureteric Junction) obstruction
  - Posterior urethral valve
  - Uretro-vesical junction (UVJ) obstruction
  - Vesicoureteric reflux
  - Abnormal polar vessels
  - Uretrocele
  - Primary megaureter
  - Neurogenic bladder
  - Severe meatal stenosis
- Acquired causes:
  - Kidney and ureteric stones
  - Blood clots
  - Retroperitoneal fibrosis
  - Urethral stricture
  - Tumors
- In children and in neonates, the relative frequency of the causes of antenatal hydronephrosis has been determined to be as follows:
  - Transient (48 %)



Figs. 2.40, 2.41, and 2.42 Abdominal CT-scan and nephrostograms showing unilateral hydronephrosis

- Physiologic (15 %)
- Ureteropelvic junction obstruction (11 %)
- Vesicoureteral reflux (9 %)
- Megaureter (4 %)
- Multicystic dysplastic kidney (2 %)
- Ureterocele (2 %)
- Posterior urethral valves (1 %)

2.4 Classification of Hydronephrosis (Figs. 2.38, 2.39, 2.40, 2.41, and 2.42)

- The widespread use of antenatal ultrasound revealed a significant structural fetal anomaly in 1 % of pregnancies.

- The probability of detecting these abnormalities depends on the experience and skills of the sonographer.
- The distribution of these anomalies is as follows:
  - 50 % involve the central nervous system
  - 20 % are genitourinary
  - 15 % are gastrointestinal
  - 8 % are cardiopulmonary
- An abnormality involving the genitourinary tract may be expected in as many as 1 in 100 pregnancies.
- The prevalence of antenatally detected hydronephrosis (ANH) is variable depending on the gestational age, diagnostic criteria and skills of the radiographer and ranges from 0.6 % to 5.4 %.
- Among the genitourinary anomalies, hydronephrosis is the commonest anomaly detected antenatally.
- The causes and distribution of antenatally diagnosed hydronephrosis are as follows:
  - Transient hydronephrosis (40–80 %)
  - Pelviureteric junction obstruction (10–30 %)
  - Vesicoureteric reflux (10–20 %)
  - Vesicoureteric junction obstruction (5–10 %)
  - Multicystic dysplastic kidney (5 %)
  - Duplex system (4–6 %)
  - Posterior urethral valve (1–2 %)
  - Others (Urethral atresia, Prune belly syndrome, etc.)
- There are several systems to grade and classify hydronephrosis.
- Hydronephrosis can be classified depending on the onset into:
  - Acute
  - Chronic
- Hydronephrosis is also classified depending on the degree of obstruction into:
  - Complete
  - Partial
- Hydronephrosis is also classified depending on the side into:
  - Unilateral
  - Bilateral
- Grading of antenatal hydronephrosis based on renal pelvis antero-posterior diameter:
  - Mild
    - Second trimester (4–6 mm)
    - Third trimester (7–9 mm)
  - Moderate
    - Second trimester (7–10 mm)
    - Third trimester (10–15 mm)
  - Severe
    - Second trimester (>10 mm)
    - Third trimester (>15 mm)

	Renal pelvis antero-posterior diameter	
Classification	Second trimester	Third trimester
Mild	4–6 mm	7–9 mm
Moderate	7–10 mm	10–15 mm
Severe	>10 mm	>15 mm

- The most common system used (Society of Fetal Ultrasound, SFU) was originally designed for grading neonatal and infant hydronephrosis:
  - Grade 0:
    - No dilatation, calyceal walls are opposed to each other
  - Grade 1 (mild):
    - Dilatation of the renal pelvis without dilatation of the calyces
    - No parenchymal atrophy
  - Grade 2 (mild):
    - Dilatation of the renal pelvis (mild) and calyces (pelvicalyceal pattern is retained)
    - No parenchymal atrophy
  - Grade 3 (moderate):
    - Moderate dilatation of the renal pelvis and calyces
    - Blunting of fornicies and flattening of papillae
    - Mild cortical thinning may be seen
  - Grade 4 (severe):
    - Gross dilatation of the renal pelvis and calyces, which appear ballooned
    - Loss of borders between the renal pelvis and calyces
    - Renal atrophy seen as cortical thinning

The Society of Fetal Ultrasound (SFU) grading of hydronephrosis

Grade	Description
Grade 0 (mild)	No dilatation, calyceal walls are opposed to each other
Grade 1 (mild)	Dilatation of the renal pelvis without dilatation of the calyces
	No parenchymal atrophy
Grade 2 (mild)	Mild dilatation of the renal pelvis and calyces
	(Pelvicalyceal pattern is retained)
	No parenchymal atrophy
Grade 3 (moderate)	Moderate dilatation of the renal pelvis and calyces
	Blunting of fornicies and flattening of papillae
	Mild cortical thinning may be seen
Grade 4 (severe)	Gross dilatation of the renal pelvis and calyces which appear ballooned
	Loss of borders between the renal pelvis and calyces
	Renal atrophy seen as cortical thinning

- The old system classify hydronephrosis in infants and children into three grades:
  - Mild
  - Moderate
  - Severe
- Obstructed hydronephrosis is also classified according to the level of obstruction:
  - Infravesical obstruction:
    - Posterior urethral valves
    - Severe meatal stenosis and phimosis
    - Severe urethral stricture
  - Supravesical obstruction:
    - Ureteropelvic junction obstruction
    - Primary megaureter
    - Uretrovesical obstruction

2.5 Clinical Features

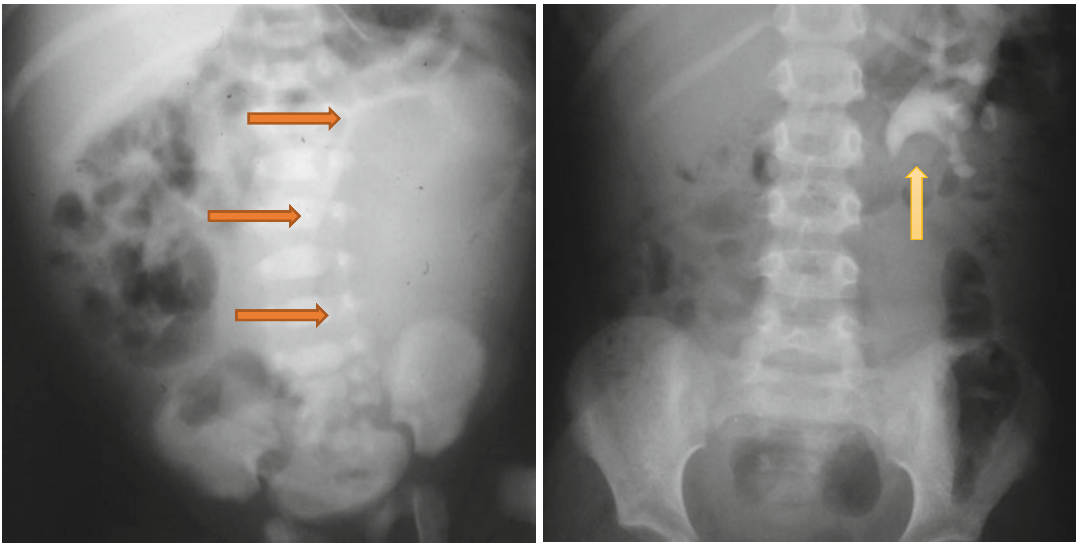
- The majority of hydronephrosis cases are now diagnosed antenattaly as a result of the widespread and routine use of antenatal ultrasound.
- Most cases of hydronephrosis in infants are incidentally detected by routine screening ultrasounds.
- Hydronephrosis diagnosed prenatally:
  - 50 % are transient and resolve spontaneously.
  - 15 % have hydronephrosis that persists but is not associated with urinary tract obstruction (non-refluxing, non-obstructive hydronephrosis). For these children, regression of the hydronephrosis occurs spontaneously, usually by age 3.
  - 35 % have a definite pathological cause for hydronephrosis. These include:
    - Pelvi-ureteric junction obstruction (11 %)
    - Vesicoureteral reflux (9 %)
    - Megaureter (4 %)
    - Multicystic dysplastic kidney (2 %)
    - Ureterocele (2 %)
    - Posterior urethral valves (1 %)
- Hydronephrosis may be asymptomatic discovered on ultrasound ordered for some other reason.
- Another presentation of hydronephrosis is urinary tract infection.
- Acute hydronephrosis secondary to a stone will cause severe flak pain.
- Chronic hydronephrosis is usually asymptomatic or cause dull aching pain.
- Other clinical presentations of hydronephrosis include:
  - Nausea and vomiting
  - Urinary tract infection with abdominal pain, fever, dysuria, nausea and vomiting.
  - Hydronephrosis secondary to obstruction at the bladder neck or urethra will lead to distension of the urinary bladder. This can cause lower abdominal pain and a palpable mass.
  - The enlarged kidney may be palpable.

Hydronephrosis Diagnosed Prenatally

- Fifty percent are transient and resolve spontaneously.
- Fifteen percent have hydronephrosis that persists but is not associated with urinary tract obstruction (non-refluxing, non-obstructive hydronephrosis).
- Thirty five percent have a definite pathological cause for hydronephrosis. These include:
  - Pelvi-ureteric junction obstruction (11 %)
  - Vesicoureteral reflux (9 %)
  - Megaureter (4 %)
  - Multicystic dysplastic kidney (2 %)
  - Ureterocele (2 %)
  - Posterior urethral valves (1 %)

2.6 Investigations and Diagnosis

- Complete blood count and differential
- Serum electrolytes
- Blood urea and creatinine
- Urine analysis and culture
- Abdominal x-ray (Figs. 2.43 and 2.44):
  - This may show a soft tissue density on the left or right lumbar regions representing the enlarged kidney.
  - Urolithiasis may cause hydronephrosis and radiopaque stones may be seen on plain abdominal x-rays.
- Abdominal and pelvic ultrasound (Figs. 2.45, 2.46, and 2.47):
  - This is important in the detection of hydronephrosis and whether it is unilateral or bilateral.
  - Ultrasound is also valuable in defining the degree of hydronephrosis.
  - The size of the renal pelvis as measured by ultrasound is an estimate of the degree of hydronephrosis in those with obstructive hydronephrosis.
  - It is also important to evaluate the ureter as dilatation of the ureter is seen in those with vesicoureteral reflux (VUR) or obstructive uropathy distal to the uretero-pelvic junction.
  - An isolated hydronephrosis without dilatation of the ureter is suggestive of pelvi-ureteric junction obstruction.
  - The ultrasound is also valuable in evaluating the renal parenchymal thickness. Sever hydronephrosis will lead thinning of the renal cortex thickness.
  - Ultrasonographic findings of posterior urethral valves are:
    - Bilateral hydrouretero-nephrosis
    - Dilated, thick walled bladder that fails to empty
    - Dilated posterior urethra
- Intravenous urogram (IVU) (Figs. 2.48 and 2.49):
  - Intravenous urography is a useful investigation to outline the anatomy of the renal system and locate the site of obstruction.
  - This is rarely used nowadays as there are other more valuable and less invasive investigations.
  - Add to this, the radiation exposure in children.
- A micturating cystourethrogram (MCU) (Figs. 2.50, 2.51, and 2.52):
  - This is performed in patients with unilateral or bilateral hydronephrosis to exclude the possibility of vesicoureteral reflux or anatomical abnormalities such as posterior urethral valves.
  - Vesicoureteral reflux is present in 8–38 % of patients with unilateral or bilateral antenatal hydronephrosis, as compared to <1 % in the general population.
  - MCU is indicated in the following conditions:
    - Infants with moderate to severe hydronephrosis (SFU grade 3–4, or renal APD >10 mm)
    - Dilated ureter(s)
    - Bladder or urethral abnormalities
    - Patients with history of milder grades of antenatal hydronephrosis who show worsening hydronephrosis, progressive parenchymal thinning or occurrence of UTI.



Figs. 2.43 and 2.44 Plain abdominal x-rays showing a soft tissue density in the left lumbar region representing enlarged hydronephrotic left kidney on the left and a large staghorn calculus on the right side

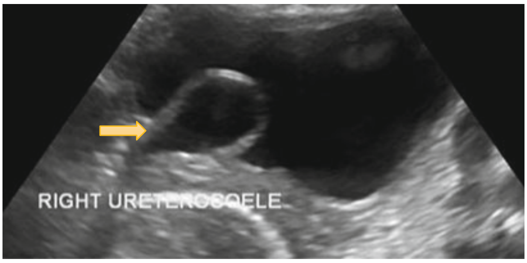


Fig. 2.45 Abdominal and pelvic ultrasound showing a right uretrocele

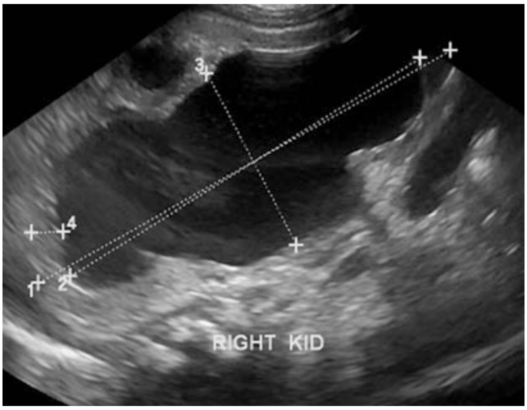


Fig. 2.46 Abdominal ultrasound showing a right hydronephrotic kidney

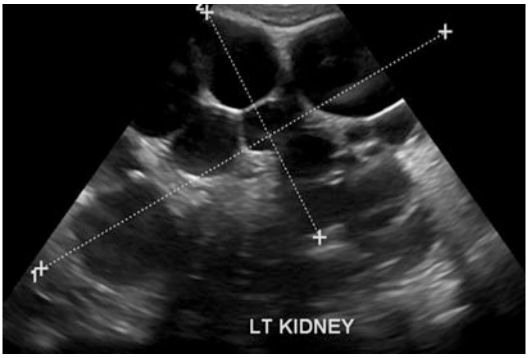
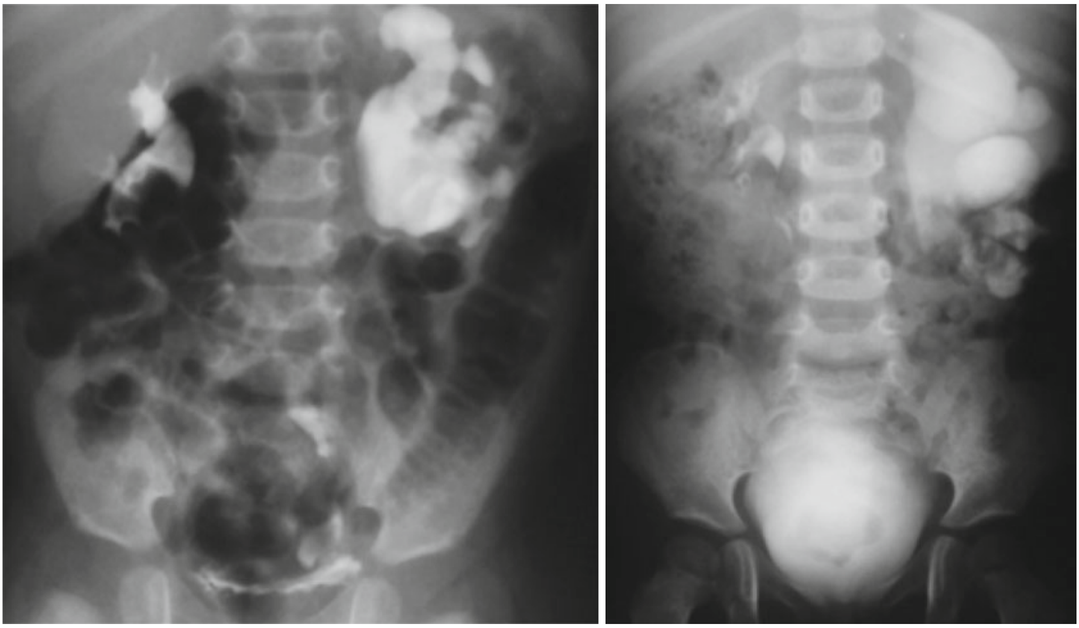
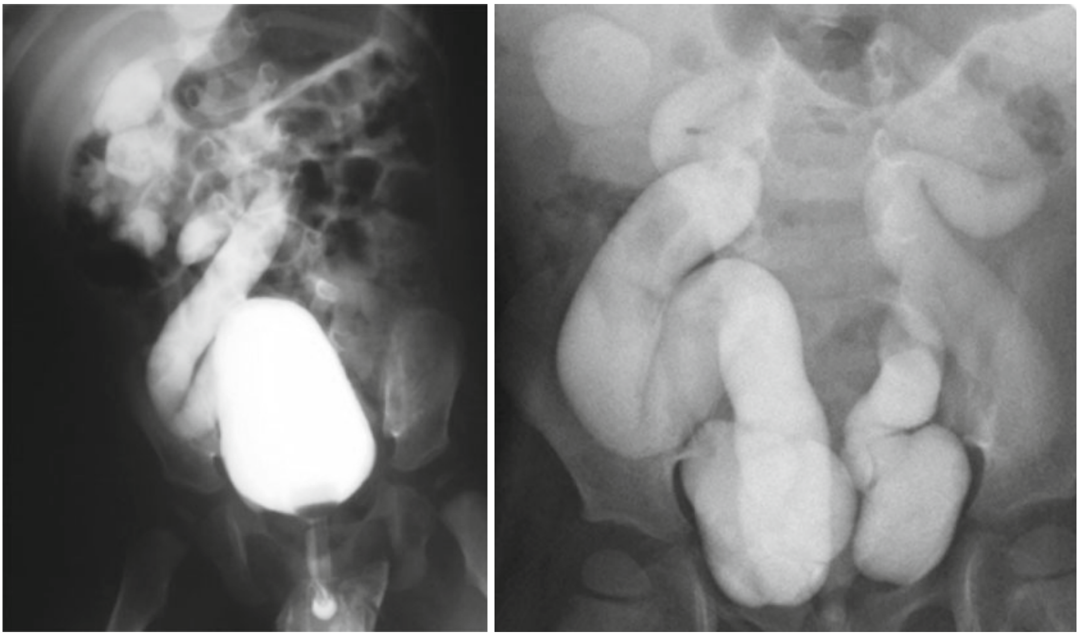


Fig. 2.47 Abdominal ultrasound showing an enlarged left multicystic kidney

- Diuretic renography (Fig. 2.53):
  - Pelviureteric junction obstruction should be considered in infants with hydronephrosis, where dilating VUR is excluded.
  - The likelihood of detecting obstruction is considerably higher in patients with SFU grade 4 or renal APD exceeding 20–30 mm.
  - The possibility of vesicoureteric junction obstruction or megaureter is considered in patients with hydronephrosis and dilated ureter where MCU is normal.
  - Patients with VUR and worsening hydronephrosis also require evaluation for pelvi-



Figs. 2.48 and 2.49 Intravenous urograms showing hydronephrotic left kidney



Figs. 2.50 and 2.51 Micturating cystourethrograms showing severe unilateral and bilateral vesicoureteral reflux. Note the dilated tortous ureters

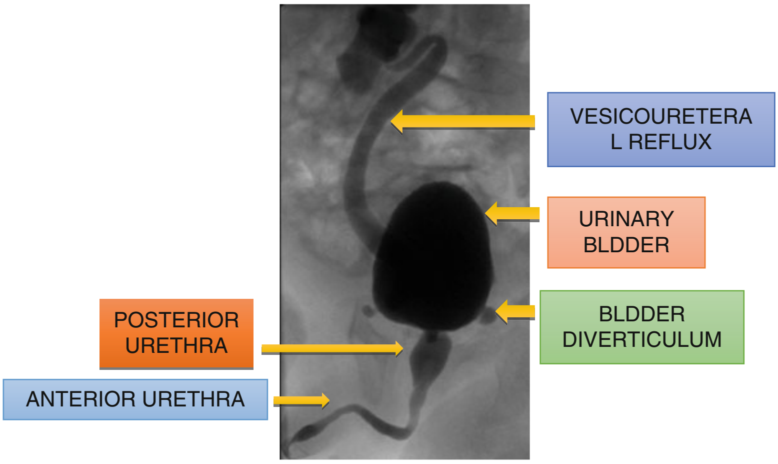
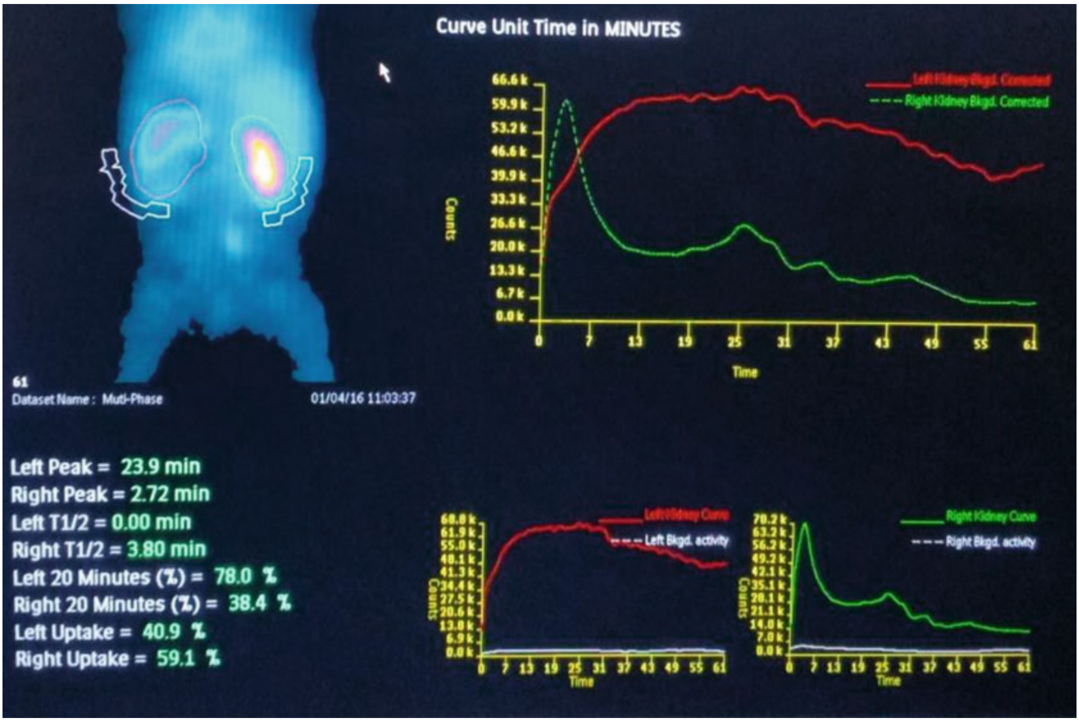

VESICOURETERA
L REFLUX
URINARY
BLDDER
BLDDER
DIVERTICULUM
POSTERIOR
URETHRA
ANTERIOR URETHRA

Fig. 2.52 A micturating cystourethrogram showing right vesicoureteral reflux. Note also the dilated posterior urethra diagnostic of posterior urethral valve. Note also the small bladder diverticulae


Curve Unit Time in MINUTES
66.6 k
59.9 k
53.2 k
46.6 k
39.9 k
33.3 k
26.6 k
20.0 k
13.3 k
6.7 k
0.0 k
Counts
0
7
13
19
25
31
37
43
49
55
61
Time
Left Kidney Bkgd. Corrected
Right Kidney Bkgd. Corrected
61
Dataset Name : Muti-Phase
01/04/16 11:03:37
68.8 k
61.9 k
55.0 k
48.1 k
41.3 k
34.4 k
27.5 k
20.6 k
13.8 k
6.9 k
0.0 k
Counts
0
7
13
19
25
31
37
43
49
55
61
Time
Left Kidney Curve
Left Bkgd. activity
70.2 k
63.2 k
56.2 k
49.2 k
42.1 k
35.1 k
28.1 k
21.1 k
14.0 k
7.0 k
0.0 k
Counts
0
7
13
19
25
31
37
43
49
55
61
Time
Right Kidney Curve
Right Bkgd. activity

```
Left Peak =  23.9 min
Right Peak = 2.72 min
Left T1/2 = 0.00 min
Right T1/2 = 3.80 min
Left 20 Minutes (%) =  78.0  %
Right 20 Minutes (%) =  38.4  %
Left Uptake =  40.9  %
Right Uptake =  59.1  %
```

Fig. 2.53 A diuretic renogram of a child with left PUJ obstruction

ureteric junction obstruction, since the two may coexist in 7–18 % of patients.

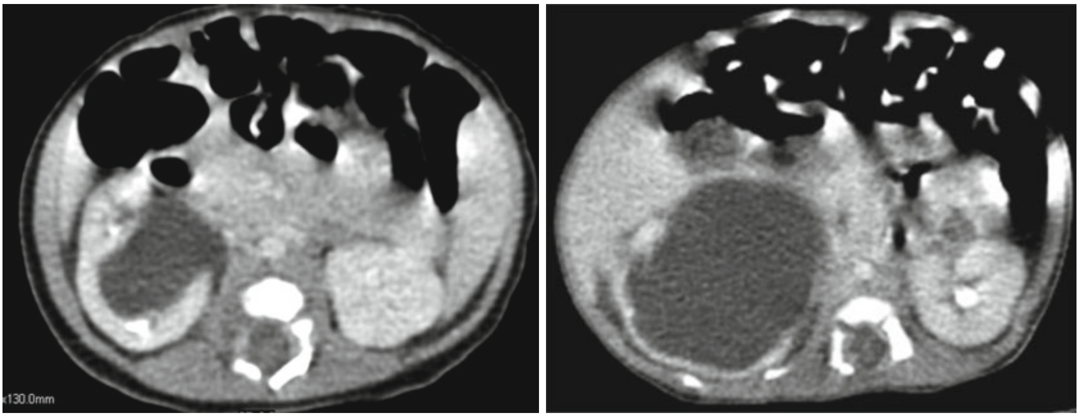
- Diuretic renography allows differentiation between obstructive and non-obstructive hydronephrosis and estimating relative renal function.
- Radiopharmaceuticals such as 99mtechnetium mercaptoacetyltriglycine (MAG3) or ethylenedicysteine (EC) are preferred, since they show greater renal extraction and higher kidney to background ratio compared to diethylenetriaminepentaacetic acid (DTPA).

- Renal urography includes the following two phases:
  - First, radioisotope is injected intravenously and renal parenchymal (cortical) uptake is measured during the first 2–3 min. The rela-

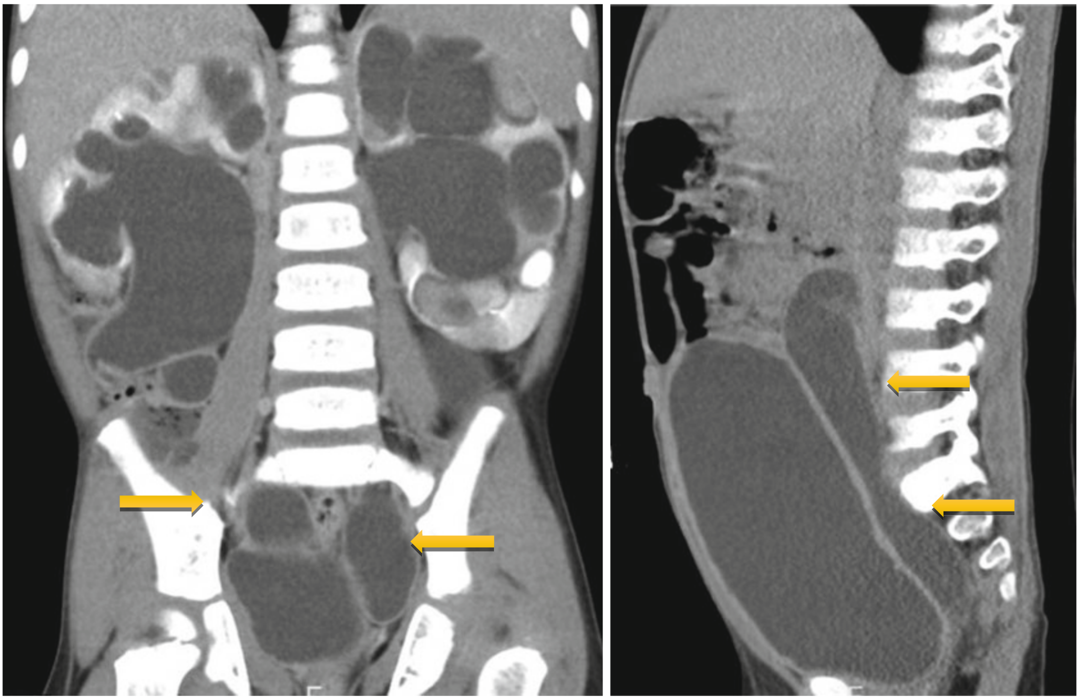
tive contribution of each kidney to overall renal function (called the split renal function) is assessed quantitatively and is useful as a baseline study.

- Second, at peak renal uptake, intravenous furosemide is administered and the excretion of isotope from the kidney is measured, referred to as the washout curve. This phase indicates the extent of obstruction, if present.
- The washout curve:
  - In a healthy kidney, furosemide administration results in a prompt washout.
  - In a dilated system, if washout occurs rapidly after diuretic administration (<15 min), the system is not obstructed.
  - If washout is delayed beyond 20 min, the pattern is consistent with obstructive uropathy.
  - However, a delayed washout must be interpreted with caution. If washout is from 15 to 20 min, the study is indeterminate.
- The split renal function:
  - Split renal function results are the most useful criteria to evaluate a decrease in renal function.
  - In patients with unilateral hydronephrosis, if the normal nonhydronephrotic kidney and hydronephrotic kidney both have equal function, conservative management without surgery is a safe option.
  - A significant decrease in renal function of one kidney is defined as 35 % or less differential renal function.
  - A decrease in differential renal function was associated with severe antenatal hydronephrosis (i.e., renal pelvic diameter >10 mm at 20–24 week gestation and >16 mm at 33 week gestation).
- A normal renogram curve is characterized by:
  - An early peak (2–5 min), rapidly descending phase and almost complete renal emptying by 20 min.
  - Drainage is influenced by state of hydration, and composite and differential kidney function.
  - The presence of satisfactory drainage spontaneously, or following IV frusemide and micturition excludes significant obstruction.
  - An obstructive pattern is defined by an ascending or plateau phase over 20 min that fails to empty following diuretic administration and on post-micturition views.
  - Estimated differential renal function values between 45 % and 55 % are considered normal.
  - An initial differential function below 35–40 % in the kidney with obstructed drainage signifies impaired renal function.
  - Other features that suggest obstruction include ipsilateral supranormal differential renal function (55 %) and prolonged time to clear 50 % of the radionuclide (t1/2 >20 min).

- Abdominal CT-scan (Figs. 2.54 and 2.55)
  - Abdominal CT-scan is valuable in outlining the extent of hydronephrosis and site of obstruction.
  - It is also useful in measuring the renal parenchyma thickness.
- Magnetic resonance urography (MRU) (Figs. 2.56, 2.57, 2.58, and 2.59):
  - MRU in children is becoming more commonly used in the diagnosis and management of congenital uropathies such as PUJ obstruction.
  - MRU is especially useful in the management of obstructed kidneys that have rotation or ascent anomalies, or are solitary.
  - MRU can more clearly define the anatomy and delineate the proper surgical approach.
  - The disadvantage of MRU is that the study often requires general anesthesia or heavy conscious sedation in children.
  - Furthermore, the contrast agent can only be used if renal function is normal because of reports of irreversible renal fibrosis in patients with renal insufficiency.
- Antegrade or retrograde pyelography is usually used to relieve, rather than diagnose, urinary tract obstruction. These tests, however, can also be performed for diagnosis when the history is highly suggestive (Figs. 2.60, 2.61, 2.62, and 2.63).



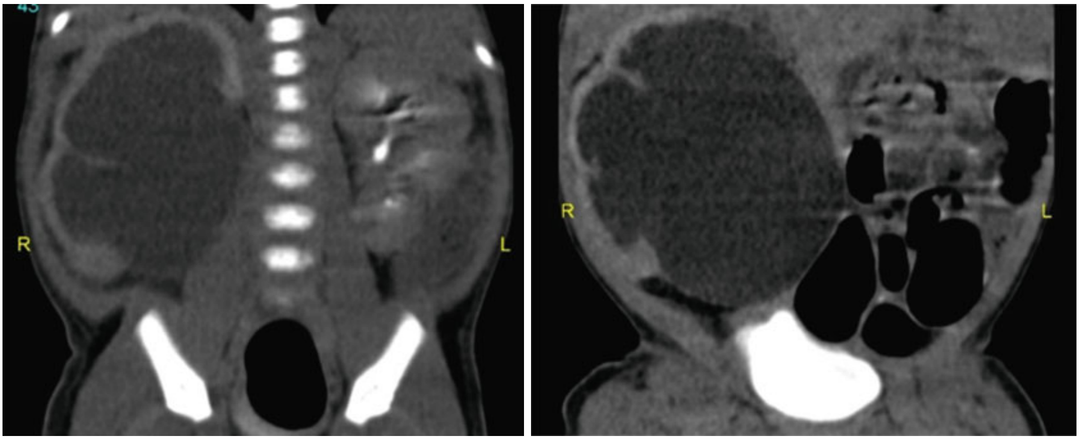
Figs. 2.54 and 2.55 Abdominal CT-scan showing hydronephrosis secondary to PUJ obstruction. Note the difference in the renal parenchyma thickness between the two patients. I the second picture, there is hardly any renal tissue remaining



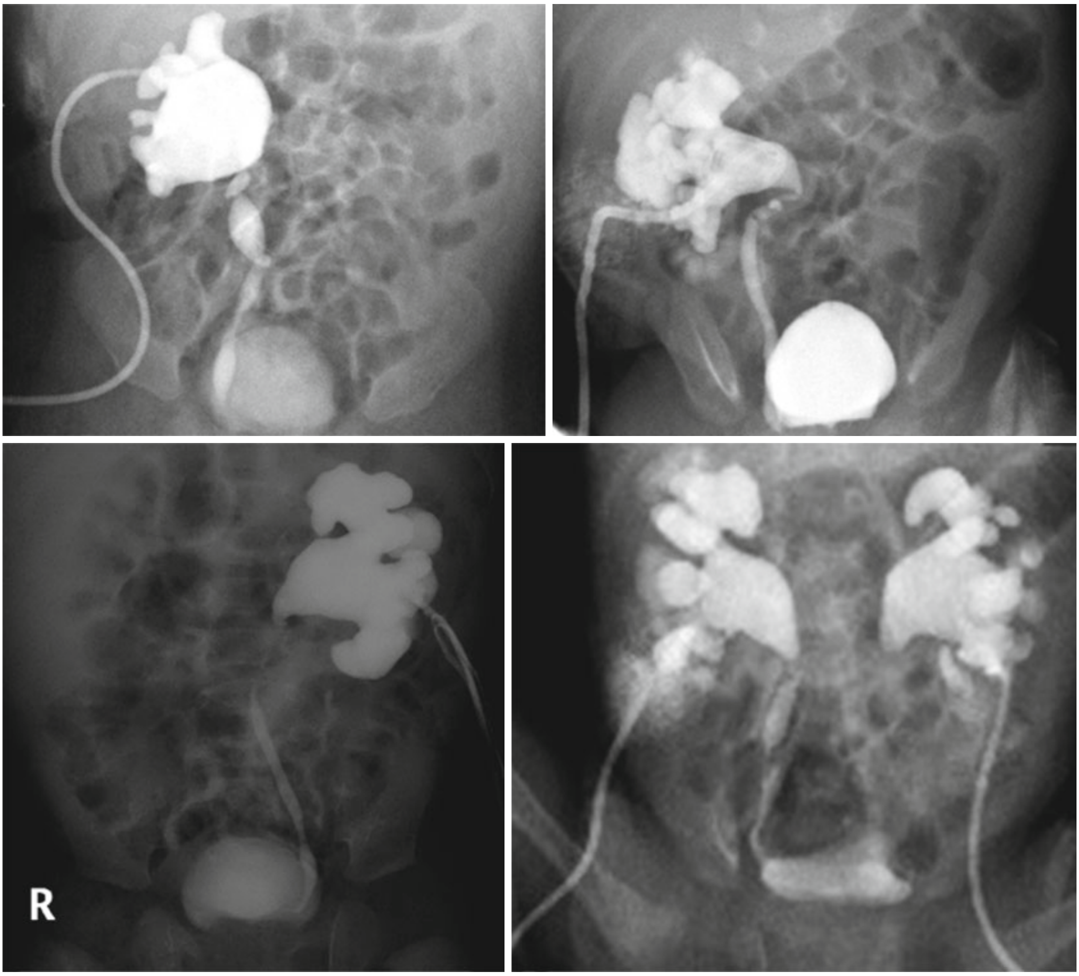
Figs. 2.56 and 2.57 MRU showing bilateral severe hydroureteronephrosis. Note the marked dilated ureters

2.7 Treatment

- The aim of treatment is to remove the obstructive cause and allow free drainage of the urine.
- The specific treatment of patients with hydronephrosis depends on the etiology and site of obstruction.
- The presence of infection should be treated aggressively as infection with hydronephrosis may progress rapidly to sepsis.
- The presence of bilateral hydronephrosis or hydronephrosis in a solitary kidney calls for urgent evaluation and management.



Figs. 2.58 and 2.59 MRU showing severe right hydronephrosis secondary to pelvi-ureteric junction obstruction. Note the compressed renal tissue



Figs. 2.60, 2.61, 2.62, and 2.63 Percutaneous nephrostograms showing unilateral and bilateral hydronephrosis secondary to PUJ obstruction

- A nephrostomy tube is a very valuable procedure to relieve acute hydronephrosis (Figs. 2.60, 2.61, 2.62, and 2.63).
- The use of ureteral stent can bypass an obstruction and temporarily relieve the pressure on the affected kidney.
- Lower urinary tract obstruction can be relieved by insertion of a urinary catheter or a suprapubic catheter.
- Fetal surgery:
  - Fetal surgery is indicated in those with antenatal severe hydronephrosis in an attempt to preserve renal function and improve the clinical outcome.
  - It is however not readily available and require expertise.
- Indication of surgical interventions in those with PUJ obstruction:
  - Conservative management is appropriate for infants with an obstructive pattern on diuretic renography and differential function exceeding 40 %.
  - While most experts suggest that pyeloplasty be considered in patients showing obstructed drainage and differential function below 40 %, others propose surgery at differential function below 35 %, or an obstructed renogram with prolonged t1/2 >20 min.
  - In those with PUJ, a reduction of differential renal function by more than 5–10 % correlates with declining renal function, and the need for pyeloplasty.
  - The presence of symptoms including pain, palpable renal mass or recurrent febrile UTI.
  - The presence of large anteroposterior diameter of renal pelvis exceeding 20–30 mm predicts the need for surgery in 50–55 % patients.
  - Surgery allows preservation of renal function in the majority of patients.
  - Predictors of unsatisfactory outcome include baseline renal differential function <30 % and anteroposterior diameter of renal pelvis >50 mm with dilated calyces.
- Antibiotic Prophylaxis
  - While there is increased risk of UTI, there is lack of evidence that antibiotic prophylaxis in patients with mild VUR confers clinical benefit.
  - Multiple studies and a systematic review suggest that the severity of antenatal hydronephrosis does not correlate with the grade of reflux, and that patients with VUR may have normal postnatal ultrasound.
  - Infants with postnatally confirmed moderate or severe hydronephrosis (SFU 3–4; renal APD >10 mm) or dilated ureter receive antibiotic prophylaxis while awaiting evaluation.
- There are those who recommend that all patients detected to have VUR receive antibiotic prophylaxis through the first year of life.
- Antibiotics that are preferred include cephalexin (10 mg/kg/day) during the first 3 months of life, and cotrimoxazole (1–2 mg/kg/day) or nitrofurantoin (1 mg/kg/day) later.
- Patients with moderate or severe hydronephrosis and/or dilated ureter should receive antibiotic prophylaxis while awaiting investigations.
- Since the risk of UTI is low with mild hydronephrosis, antibiotic prophylaxis is not necessary in these infants.

2.8 Antenatal Hydronephrosis

- The widespread use of antenatal ultrasound has resulted in an increase in the early detection of antenatal hydronephrosis.
- Fetal hydronephrosis (dilatation of the renal pelvis with or without dilation of the renal calyces) is a common, readily diagnosed finding on antenatal ultrasound examination and can be detected as early as the 12th–14th week of gestation.
- Although antenatal hydronephrosis is most often transient or clinically insignificant, urinary tract obstruction or vesicoureteral reflux (VUR) are important causes that should be diagnosed soon after birth because they may result in renal impairment or cause further renal damage.
- The risk of significant renal and urinary tract abnormality in those with hydronephrosis increases with:

  - The severity of hydronephrosis
  - Persistence of hydronephrosis into the third trimester
  - Bilateral involvement
  - The presence of oligohydramnios
- Once fetal hydronephrosis is detected, the following parameters need to be evaluated using ultrasonography:
  - Severity of hydronephrosis
  - Whether hydronephrosis is unilateral or bilateral
  - Dilatation of the ureter
- The risk of postnatal renal pathological changes correlates with the degree of antenatal hydronephrosis as follows:
  - The risk for those with mild hydronephrosis is 12 %
  - The risk for those with moderate hydronephrosis is 45 %
  - The risk for those with severe hydronephrosis is 88 %
- The severity of antenatal hydronephrosis correlates positively with:
  - Persistent postnatal hydronephrosis
  - The need for surgical intervention
  - The risk of UTI
- Grading the severity of antenatal hydronephrosis is important as this enables identification of infants that require close follow-up.
- About 88 % of mild antenatal hydronephrosis resolve in utero or in the neonatal period.
- It has been estimated that one in three neonates with moderate to severe hydronephrosis persisting in the third trimester required postnatal surgery.
- Hence, an ultrasound in the third trimester is valuable for identifying fetuses that require postnatal evaluation, follow up and possibly surgery.
- A systematic review concluded that:
  - 98 % of patients with SFU grade 1–2 or antero-posterior diameter (APD) of the renal pelvis <12 mm resolved.
  - 51 % of patients with APD >12 mm or SFU 3–4 resolved.
- All newborns with history of antenatal hydronephrosis should have postnatal ultrasound examination within the first week of life.
- Ultrasonography should be performed early, within 24–48 h of birth for neonates with:
  - Suspected posterior urethral valves
  - Oligohydramnios
  - Severe bilateral hydronephrosis
  - Severe hydronephrosis in a solitary kidney

Pathological Causes of Antenatally Diagnosed Hydronephrosis

- Isolated Unilateral hydronephrosis
  - PUJ
- Unilateral hydronephrosis with hydroureter
  - Uretro-esical junction obstruction
  - Uretrocele
  - Vesicoueteric reflux
  - Posterior urethral valve
- Isolated bilateral hydronephrosis
  - Bilateral PUJ
- Bilateral hydronephrosis with hydroureter
  - Bilateral uretro-vesical obstruction
  - Bilateral vesicoureteric reflux
  - Posterior urethral valve
  - Bilateral uretrocele
  - Urethral stricture

- In all other cases, the ultrasound should be performed preferably within 3–7 days, or before hospital discharge.
- A single ultrasound in the first few days of life might not detect all abnormalities of the kidneys or urinary tract, due to low urine flow secondary to dehydration and low glomerular filtration rate. An ultrasound at 6 weeks is more sensitive and specific for obstruction, than that in the first week of life.
- Postnatal radiologic studies:
  - Postnatal radiologic evaluation of a newborn with antenatal hydronephrosis begins with an ultrasonography examination.
  - The timing of ultrasonography and the need for other studies depend on the severity of postnatal hydronephrosis and whether

there is bilateral involvement or an affected solitary kidney.

  - The timing of the study depends on the severity of the antenatal hydronephrosis.
    - In general, examination should be avoided in the first 2 days after birth because hydronephrosis may not be detected because of extracellular fluid shifts that underestimate the degree of hydronephrosis.
    - However, infants with bilateral hydronephrosis and those with a severe hydronephrotic solitary kidney require urgent evaluation on the first or second postnatal day because of the increased likelihood of significant disease and a possible need for early surgical intervention.
    - For those with unilateral hydronephrosis without antenatal bladder pathology, performing postnatal sonography 1–4 weeks after birth is recommended.
  - A voiding cystourethrography (VCUG) is performed to detect VUR and, in boys, to evaluate the posterior urethra.

Postnatal Hydronephrosisultrasound Evaluation

- The severity of hydronephrosis postnatally is determined by a renal ultrasound performed after 48 h of life in a full term infant and is based on anterior posterior pelvic diameter as follows:
  - <7 mm should be considered normal
  - 7–8 mm: Mild hydronephrosis
  - 9–15 mm: Moderate hydronephrosis
  - >15 mm: Severe hydronephrosis. These infants are at the greatest risk for significant renal disease, which requires surgical correction.

- Diuretic renography:
  - This is used to diagnose urinary tract obstruction in infants with persistent hydronephrosis.
  - It is usually ordered after a VCUG has demonstrated no vesicoureteral reflux.
  - It measures the drainage time from the renal pelvis and assesses total and individual kidney function.
  - The preferred radioisotope is technetium Tc 99m-mercaptoacetyltriglycine (Tc99m MAG3), which is taken up by the renal cortex, filtered across the glomerular basement membrane to the renal tubules, and excreted into the renal pelvis and urinary tract.

- The management of infants with antenatal hydronephrosis depends on:
  - Confirmation of persistent postnatal hydronephrosis
  - The severity of hydronephrosis: Fetuses with a renal pelvic diameter greater than 15 mm during the third trimester are at the greatest risk for significant renal disease
  - Whether hydronephrosis is bilateral or unilateral
  - Whether hydronephrosis is in a solitary kidney or not
- Bilateral hydronephrosis:
  - Infants with severe bilateral antenatal hydronephrosis and/or bladder distension are at increased likelihood of having significant disease.
  - These infants and those with a severe hydronephrotic solitary kidney should be evaluated initially by ultrasonography on the first postnatal day.
  - Bilateral hydronephrosis suggests an obstructive process at the level of or distal to the bladder, such as uretrovesical obstruction, ureterocele or posterior urethral valves (PUV) in a male infant, which can be associated with impaired renal function and ongoing renal injury.
  - If postnatal ultrasonography demonstrates persistent hydronephrosis, voiding cystourethrography (VCUG) should be performed. In male infants, the posterior urethra should be fully evaluated to detect possible PUVs.

  - Infants with mild or moderate hydronephrosis can be evaluated after 7 days of life.
- Severe unilateral hydronephrosis:
  - In newborns with severe antenatal unilateral hydronephrosis (renal pelvic diameter >15 mm in the third trimester), ultrasonography should be performed after age 48 h and within the first 2 weeks of life).
- Moderate and mild unilateral hydronephrosis:
  - In newborns with less severe antenatal unilateral hydronephrosis (renal pelvic diameter <15 mm during third trimester), ultrasonography can be performed after age 7 days to see whether the hydronephrosis has persisted postnatally.
  - Moderate hydronephrosis (renal pelvic diameters between 10 and 15 mm) resolves by age 18 months in most cases. Resolution was defined as renal pelvic diameter ≤5 mm on two consecutive ultrasounds.
- Antibiotic prophylaxis:
  - The frequency of urinary tract infections has been reported to be higher in children with prenatally diagnosed hydronephrosis when compared with the general pediatric population.
  - The risk of urinary tract infection rises if there is an underlying urologic abnormality, such as VUR or obstructive uropathy.
  - The risk of urinary tract infection is greater in girls than boys.
  - Infants with severe hydronephrosis are at greater risk for an underlying urologic abnormality and should receive antibiotic prophylaxis after delivery until the diagnosis of VUR or obstructive uropathy is excluded.
  - Children with mild or moderate hydronephrosis confirmed postnatally should also receive antibiotic prophylaxis (amoxicillin, 12–25 mg/kg given orally per day) until the diagnosis of VUR has been made or eliminated.
  - Antibiotic prophylaxis is not indicated in infants with normal postnatal ultrasonography findings or in those with mild hydronephrosis.
  - It was found that infants with high-grade hydronephrosis receiving continuous antibiotic prophylaxis had significantly lower urinary tract infections when compared to those who did not receive prophylactic antibiotics (14.6 % vs 28.9 %).
  - This however is not the case for infants with low-grade hydronephrosis were the frequency of urinary tract infections were similar (2.2 % vs. 2.8 %).
  - Other indications for prophylactic antibiotics include:
    - The presence of ureteral dilation
    - Associated high-grade VUR
    - Ureterovesical junction obstruction
  - In patients with low-grade hydronephrosis (SFU grades I and II), there was no difference in the rate of UTI between patients treated with continuous antibiotic prophylaxis and those who were not treated.
  - Patients with high-grade hydronephrosis (SFU grades III and IV) who received continuous antibiotic prophylaxis had a lower rate of UTI compared with those who were not treated with antibiotics.
  - Infants with persistent severe postnatal hydronephrosis should have a VCUG to detect VUR.
    - VUR accounts for approximately 9 % of cases of antenatal hydronephrosis, but it is more common and severe in infants with persistent postnatal hydronephrosis (13–30 %).
    - Infants who have VUR demonstrated on VCUG should remain on antibiotic prophylaxis.
    - If the VCUG does not show reflux, antibiotics are discontinued.
- Surgical management:
  - The specific treatment of an infant with hydronephrosis and hydroureter depends on the etiology.
  - There is no good evidence to support that antenatal surgery in fetuses with sono-

graphic findings consistent with urinary tract obstruction improves renal outcome.

- Signs of infection within the obstructed system warrant urgent intervention because infection with hydronephrosis may progress rapidly to sepsis.
- Bilateral Hydronephrosis with or without hydroureter and hydronephrosis in a solitary kidney calls for early evaluation and possible surgical intervention.
- Urethral catheterization is important to help rule out a lower urinary tract cause for hydronephrosis and hydroureter.
- Difficulty in passing a Foley catheter may suggest urethral stricture or bladder neck contracture.
- A percutaneous nephrostomy tube:
  - This is useful in confirming and locating the site of obstruction.
  - It is also useful in draining the obstructed kidney and reliving the pressure on the renal parenchyma.
  - It is also a useful measure to drain the kidney and buy time for the infant to grow in preparation for surgical intervention.
  - Add to this the fact that the ureter in those patients with pelviureteric junction obstruction is small which makes it difficult to reconstruct the PUJ.

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Pelviureteric Junction (PUJ) Obstruction

3

3.1 Introduction

- Pelviuureteric junction (PUJ) obstruction is a partial or complete blockage of the flow of urine from the renal pelvis into the ureter (Fig. 3.1).
- This results in accumulation of the urine in the renal pelvis leading to its dilatation and back pressure on the renal parenchyma leading to progressive renal damage and deterioration.
- PUJ obstruction is the most common cause of antenatally detected hydronephrosis and the most common cause of pediatric hydronephrosis.
- Ultrasonography reveals fetal upper urinary tract dilatation in approximately 1 in 100 pregnancies; however, only 1 in 500 are later diagnosed with significant urologic problems.
- PUJ obstruction is found in approximately 50 % of patients diagnosed with antenatal hydronephrosis.
- The reported incidence of PUJ obstruction is 1 in 500 live births. Others report the estimated incidence of PUJ obstruction as 1 per 1,000–2,000 live newborns.
- The widespread use of antenatal ultrasonography has contributed to an increase in the number and earlier diagnosis of hydronephrosis.
- PUJ obstruction is commonly seen in infants and children and less commonly in adults.
- PUJ obstruction is found more commonly in boys than in girls. The male-to-female ratio of UPJ obstruction is 3–4:1.
- PUJ obstruction occurs more on the left side than on the right. The left kidney is affected in 67 % of cases and the right kidney in 33 % of the cases.
- Bilateral PUJ obstruction is seen in about 10 % of the cases. Bilateral PUJ obstruction (synchronous and asynchronous) is seen in 10–40 % of infants <6 months.
- Less than 5 % of patients with bilateral PUJ require bilateral repair because of spontaneous resolution in a significant number of cases.
- With the current routine use of antenatal ultrasound, most cases of congenital pelviureteric junction obstruction are diagnosed antenatally.
- PUJ obstruction may be diagnosed at any age.
  - Some of these cases may be asymptomatic discovered incidentally during evaluation of some other unrelated problem.
  - PUJ may be identified during the investigation of intermittent flank or abdominal pain, urinary tract infection, hematuria.
  - Symptomatic cases may present with intermittent flank or abdominal pain that is made worse by drinking large amounts of fluids or they may present with an abdominal or flank swelling.
- The cause is usually a congenital abnormality in the pelviureteric junction leading to its narrowing.
- Other causes of intrinsic PUJ obstruction include:

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A.H. Al-Salem, *An Illustrated Guide to Pediatric Urology*, DOI 10.1007/978-3-319-44182-5_3

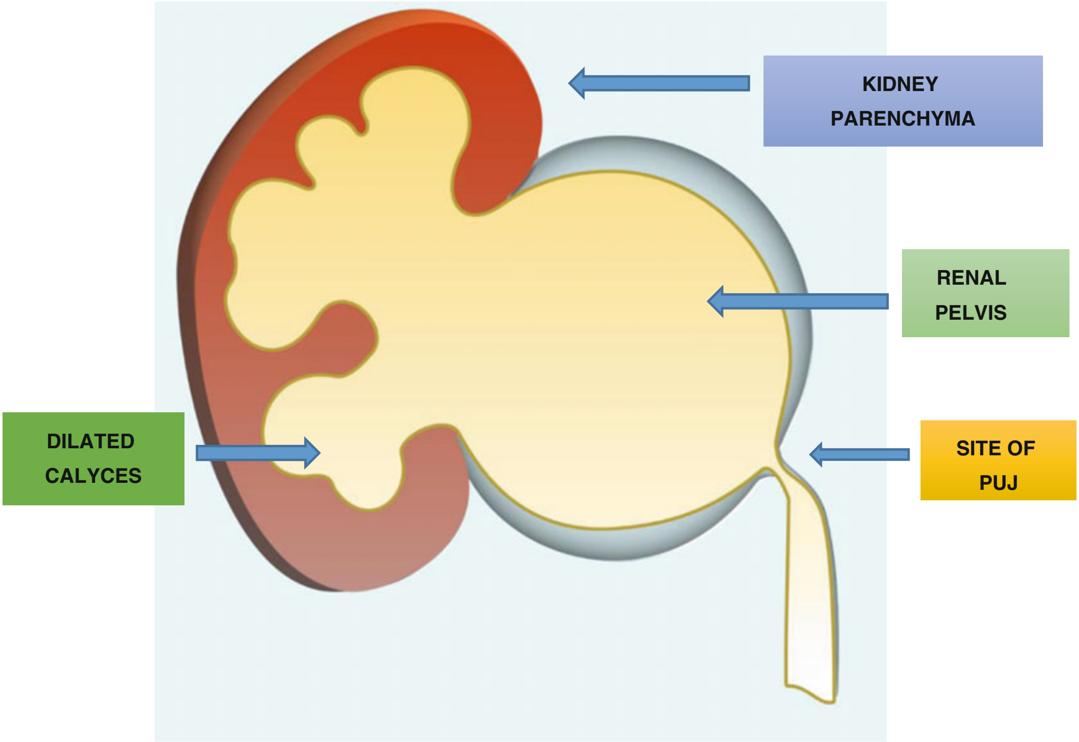


Fig. 3.1 Diagrammatic representation of PUJ obstruction (Note the dilated renal pelvis and calyces of the kidney and the area of narrowing that usually causes partial obstruction to the flow of urine from the renal pelvis to the ureter)

  - Valvular mucosal folds
  - Persistent fetal ureteral convolutions
  - Ureteral polyps
- In about 10 % of children with PUJ obstruction, an aberrant or accessory renal artery or arterial branch may cross the lower pole of the kidney, resulting in compression of the PUJ and blockage of urinary flow.
- In some cases, the obstruction may be acquired following injury to the pelviureteric junction leading to its narrowing. This is usually secondary to inflammation related to a stone stuck at the junction.
- PUJ obstruction is known to be associated with other urological anomalies and these include:
  - Renal dysplasia
  - Contralateral multicystic dysplastic kidney
  - Contralateral renal agenesis
  - Duplicated renal collecting system, in which case the lower pole system is usually the obstructed segment
  - Horseshoe kidney
  - Ectopic kidney
  - Vesicoureteral reflux (up to 40 %)
- The degree of obstruction is variable ranging from mild to severe.
- Mild degrees of PUJ obstruction do not require any surgical treatment, and these patients can be followed up hoping for complete spontaneous relive of obstruction.
- Symptomatic patients and those with impaired renal function require surgical intervention to preserve the remaining function of the kidney.
- The first reconstruction of an obstructed kidney was made in the late 1800s by Trendelenburg.
- In 1936, Foley described the YV-plasty to repair PUJ.
- In 1946, Anderson and Hynes described their operation to treat PUJ obstruction. This is now the standard operation used to repair PUJ obstruction and bear their name (The Anderson-Hynes dismembered pyeloplasty).

3.2 Embryology

- The ureter develops from the ureteral bud.
- It extends upward towards the developing kidney.
- Induction of the metanephric blastema has been thought to be mediated by the ureteral bud through several factors including:
  - Transcription factors such a Pax-2
  - Growth factors such as c-ret, kdn-1, and wt1
  - Transforming growth factor β (TGFβ).
- Embryologically, the pelvi-ureteric junction forms usually around the fifth week of intrauterine life.
- At around the 10th–12th weeks of intrauterine life, the initial solid tubular lumen of the ureter becomes reanalyzed.
- It has been suggested that the ureteropelvic and ureterovesical portions of the ureter are the last to canalize.
- Failure of canalization or partial canalization is thought to be the main embryological explanation of a PUJ obstruction.
- Another theory suggests arrest of ureteral wall musculature development leading to the persistence of an aperistaltic segment at the PUJ level leading to partial obstruction.
- Another theory suggests improper innervation with diminished synaptic vesicles at the PUJ which may play a role in the development of PUJ obstruction. This was supported by the findings of decreased amounts of the several factors in the resected specimens of PUJ. These include:
  - Protein gene product (PGP) 9.5 (a general neuronal marker)
  - S-100 protein (a nerve supporting cell marker)
  - Synaptophysin (a synapse vesical marker)
  - Nerve growth factor receptor
- Early in the embryological development, the proximal ureter is folded on itself and persistence of the unfolding may contribute to the kinked appearance of the proximal ureter.
- The most attractive theory is that the PUJ obstruction is secondary to muscular discontinuity. This disrupts the coordinated smooth muscles movement and disrupt peristalsis propagation across the PUJ. The end result is a narrow but structurally patent lumen at the PUJ which in the presence of high urine volume cannot efficiently empty. This is supported by the followings:
  - The findings of rearrangement and widely separated smooth muscle cells
  - The findings of excessive collagen fibers
  - The findings of increased elastin in the adventitia
  - The findings of diminution of nerve terminals and nerves at the stenotic portion.

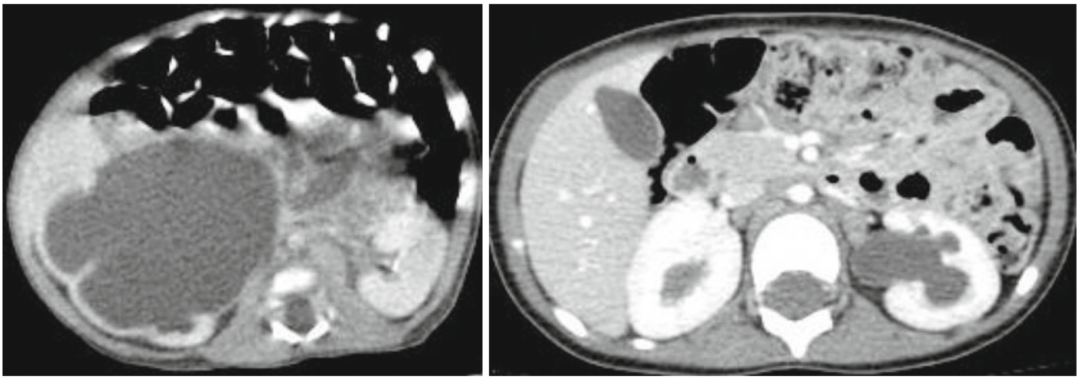
3.3 Pathophysiology

- The drainage of urine from the renal pelvis to the ureter depends on several factors.
  - Pressure within the renal pelvis is determined by the volume of urine produced
  - The internal diameter of the PUJ and collecting system
  - The compliance of renal pelvis
  - The peristaltic activity of the ureter
- In response to the increased urinary volume and pressure, the renal pelvis dilates.
- The effect of this on the renal parenchyma may be quite variable.
- Sometimes and despite of massive dilation of the renal pelvis, preservation of renal function may occur.
- A pressure-dependent flow:
  - This is seen in those with intrinsic obstruction where at low urinary flow rates, no obstruction exists; but as the urinary flow rate increases, urinary stasis will develop leading to dilatation of the renal pelvis.
- A volume-dependent flow:
  - This is seen in those with extrinsic obstruction usually caused by aberrant vessels. There is a normal urine flow which is impeded only after a definite amount of urine is collected in the renal pelvis.
  - Patients with extrinsic obstructions tend to present late in childhood, with intermittent abdominal or flank pain.

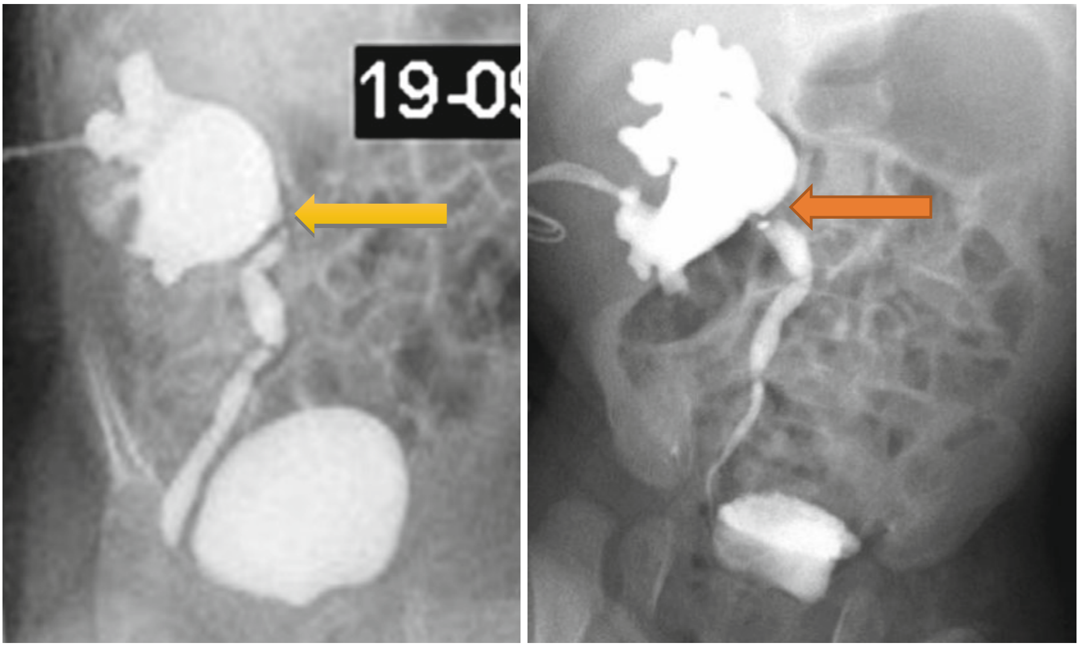
  - The degree of renal damage generally is less than that of intrinsic obstruction because the pressure damage is only evident intermittently.
- This obstructive nephropathy is progressive if the PUJ obstruction is not relived and this manifest in progressive deterioration of the renal function (Figs. 3.2 and 3.3).
- Sometimes, the obstructive nephropathy will progress and becomes irreversible in spite of relive of the PUJ obstruction.
- There is also activation of the renin-angiotensin system and administration of the angiotensin-converting enzyme (ACE) inhibitors has been shown to maintain renal blood flow and prevent the histologic changes of glomerulosclerosis.
- The long-term effects of PUJ obstruction on the kidney are quite variable and depend on several factors including:
  - The variability in the degree of obstruction
  - The timing of the obstruction
  - The ability of the renal pelvis and renal collecting system and renal parenchyma to adjust to the changes associated with obstruction.
  - Early PUJ obstruction causes severe malformation of the kidney (dysplasia), whereas late occurring PUJ obstruction may not affect the kidney as severely.

3.4 Etiology of PUJ Obstruction

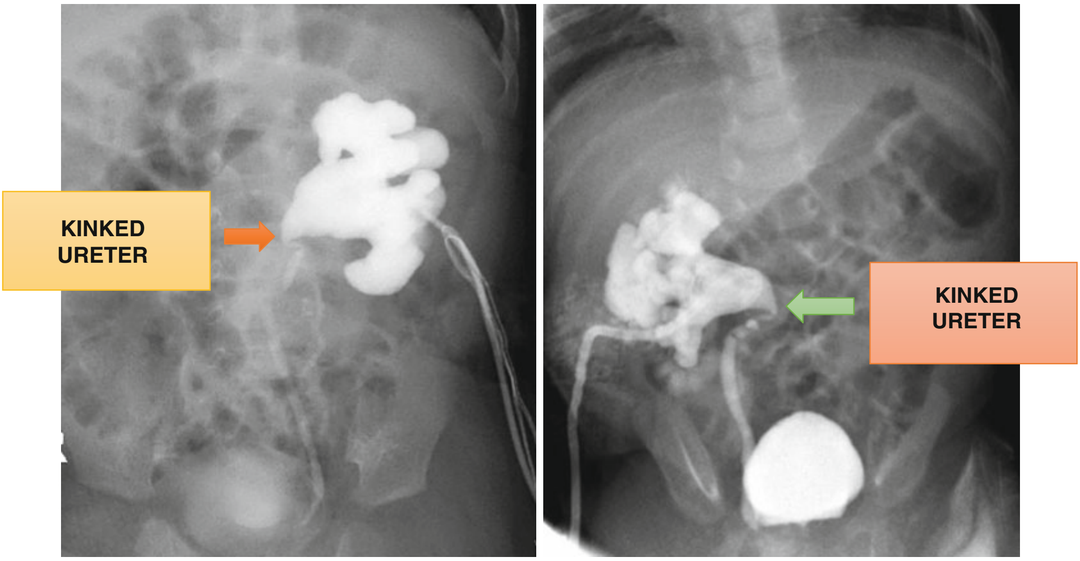
- There are several causes of PUJ obstruction and these can be divided into two groups, primary and secondary causes.
- Primary causes include (Figs. 3.4 and 3.5):
  - Intrinsic obstruction from stenosis at the PUJ due to scarring of ureteral valves.
  - An abnormal or high insertion of the ureter into the renal pelvis. This is controversial ad many consider this a secondary phenomenon to obstruction.
  - Ureteral hypoplasia may result in abnormal peristalsis through the PUJ.
  - Asymmetry of ureteral wall musculature may inhibit the natural peristaltic emptying of the renal pelvis into the ureter.
- Secondary causes include (Figs. 3.6, 3.7, 3.8, 3.9, 3.10, 3.11 and 3.12):
  - Crossing lower-pole renal vessel(s).
  - Fibrous bands
  - Kinks
  - Horseshoe or pelvic kidney
  - Duplex collecting systems
  - Rotational abnormalities of the kidney
  - Renal hypermobility can cause intermittent obstruction that is solely dependent on the position of the kidney relative to the ureter.
  - Secondary PUJ obstruction can be caused by prior surgical intervention to treat other renal disorders (e.g., renal stone)



Figs. 3.2 and 3.3 Abdominal CT-scan in two children with PUJ obstruction (Note the sever renal atrophy in the first CT as a result of progressive dilatation of the renal pelvis and pressure on the renal parenchyma while in the second one there is relative preservation of the renal parenchyma)

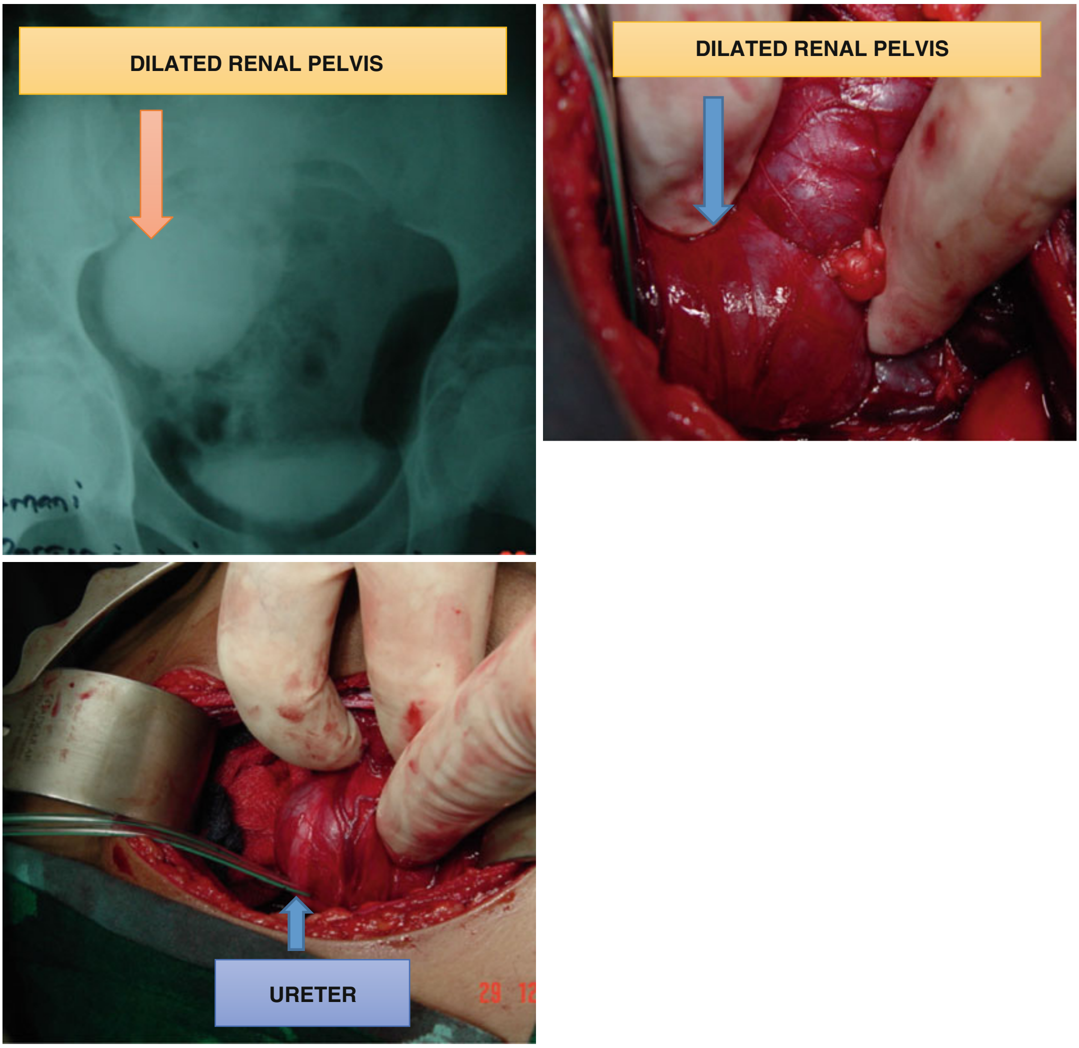


Figs. 3.4 and 3.5 Contrast studies through a nephrostomy tube for two children with PUJ obstruction (Note the normally inserted ureter in the right picture and the highly inserted ureter in the left picture. Many feel that the high insertion of the ureter is secondary to the dilated renal pelvis rather the primary cause of PUJ obstruction)



Figs. 3.6 and 3.7 Contrast studies through a nephrostomy tube in two children with PUJ obstruction (Note the kinked ureters in both but it is difficult to decide whether this is the cause or it is secondary to PUJ obstruction)

– Failed repair of a primary PUJ obstruction.
– Inflammation at the PUJ secondary to an obstructing stone.
– Ureteral-wall and periureteral scar formation as a result of inflammation or prior surgical repair.

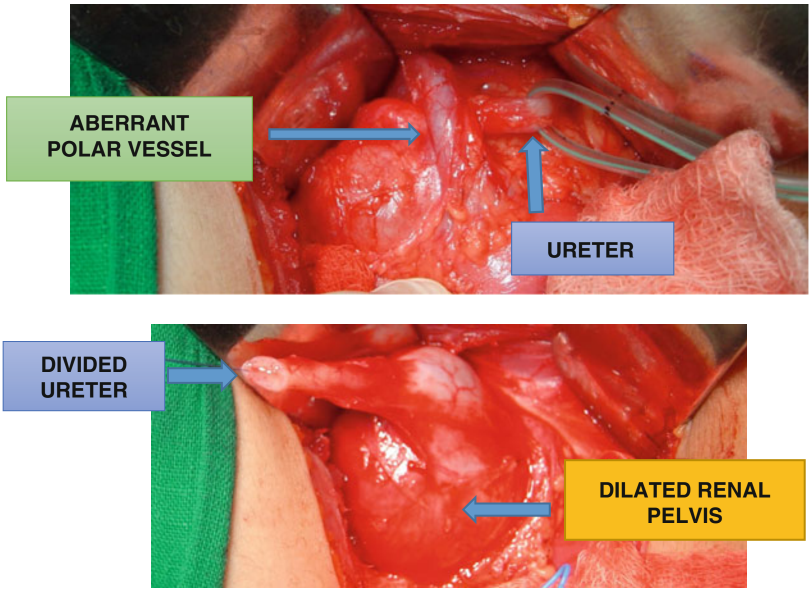


Figs. 3.8, 3.9, and 3.10 A contrast study and intraoperative photographs of a child with a hydronephrotic pelvic kidney secondary to PUJ obstruction that was also malrotated

- Aberrant polar vessels may also cause compression and obstruction of the PUJ.
- The end result of PUJ obstruction depends on the severity of obstruction. This will lead to the following changes:
  - Impaired urinary drainage
  - Elevated intrarenal back pressure
  - Dilatation of the renal pelvis and collecting system, and hydronephrosis
  - Back pressure on the renal parenchyma
  - Progressive renal damage and renal deterioration

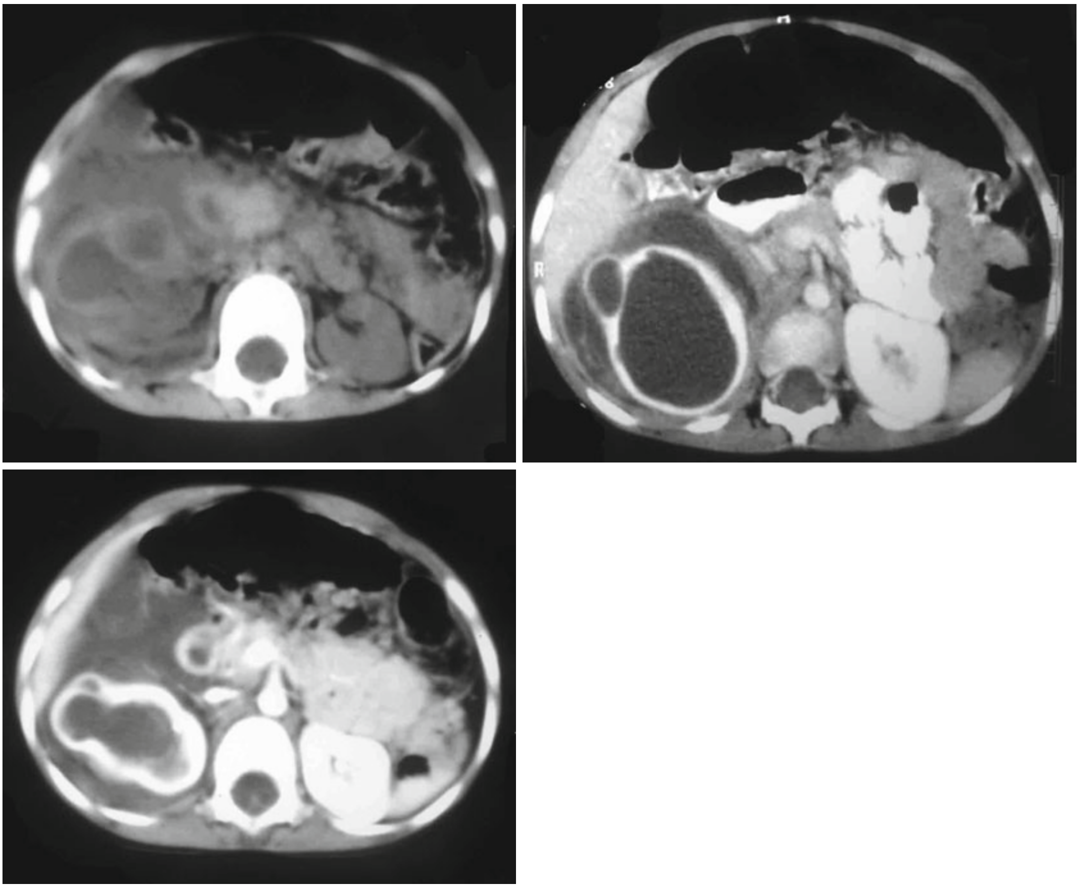
3.5 Clinical Features

- PUJ obstruction is the most common cause of neonatal and antenatal hydronephrosis, occurring in 1 per 1,000–1,500 live births.
- The presentation of PUJ obstruction is also variable.
- Neonates with PUJ obstruction are usually asymptomatic and the majority present with hydronephrosis that was diagnosed in utero by an antenatal ultrasound.



Figs. 3.11 and 3.12 Intraoperative photographs showing hydronephrosis secondary to an aberrant lower polar vessel. Note the vessel compressing the ureter in the upper photograph. Note also the associated hydronephrosis following division of the ureter

- Prior to the use of prenatal ultrasonography, most patients with PUJ obstruction present with:
  - Pain
  - Hematuria
  - Urinary tract infection
  - Failure to thrive
  - A palpable mass
- Currently, with the availability and routine use of prenatal ultrasonography, urologic abnormalities including PUJ obstruction are being diagnosed earlier and more frequently.
- 50 % of patients diagnosed with antenatal hydronephrosis are eventually diagnosed with PUJ obstruction upon further workup.
- Fetal and neonatal hydronephrosis:
  - Most cases of PUJ obstruction are diagnosed antenatally during routine antenatal ultrasound.
  - These cases are confirmed by postnatal ultrasound.
  - Newborns may present with:
    - A palpable abdominal mass caused by an enlarged obstructed kidney.
    - Urinary tract infection
    - Hematuria
    - Failure to thrive
    - Renal failure is an unusual presentation, and occurs in infants with a single obstructed kidney or with bilateral severe hydronephrosis.
- Older children may present with:
  - The presentation of patients with PUJ is variable depending on the severity of obstruction.
  - Intermittent back pain, flank pain or abdominal pain
  - The pain may worsen during brisk diuresis
  - Abdominal pain may be accompanied by nausea and vomiting
  - A detailed history may reveal that the pain correlates with periods of increased fluid intake or ingestion of a food with diuretic properties (i.e. Dietl's crisis).
  - Urinary tract infection
  - A flank mass representing the hydronephrotic kidney
  - The enlarged kidney is vulnerable to traumatic injury (Figs. 3.13, 3.14 and 3.15)
  - Hematuria
  - Renal calculi
  - Hypertension
  - An incidental finding on abdominal ultrasound evaluation



Figs. 3.13, 3.14, and 3.15 Abdominal CT-scans showing trauma and rupture of a hydronephrotic kidney in a child with PUJ obstruction

- Initially, most children diagnosed to have PUJ obstruction are treated conservatively and monitored closely.
- Surgical intervention is indicated in symptomatic patients and those with significantly impaired renal drainage and decreased renal function.
- The presence of significant hydronephrosis on antenatal ultrasound is based on the followings:
  - The anteroposterior diameter of the renal pelvis is more than 10 mm.
  - The ratio of the renal pelvis to the anteroposterior kidney is more than 0.3.
  - Evidence of caliectasis is present after 24 weeks of gestation.
- A follow-up postnatal ultrasound should be performed 36–48 h after birth to avoid the transient neonatal dehydration.
- Earlier postnatal ultrasound (24–48 h) is performed for those with severe PUJ obstruction.
  - Those with very large renal pelvis
  - Those with bilateral hydronephrosis
  - Those with solitary kidney
  - Those with PUJ obstruction and oligohydramnios
- The most widely used grading system of the severity of hydronephrosis on ultrasonography after birth is SFU (Society for Fetal Urology) system, rather than the anteroposterior diameter of the renal pelvis.
- The SFU grading system for hydronephrosis is as follows :
  - Grade 0:
    - No hydronephrosis, intact central renal complex seen on ultrasonography
  - Grade 1:

    - Only renal pelvis visualized, dilated pelvis on ultrasonography, no caliectasis
  - Grade 2:
    - Moderately dilated renal pelvis and a few calyces
  - Grade 3:
    - Hydronephrosis with nearly all calyces seen, large renal pelvis without parenchymal thinning
  - Grade 4:
    - Severe dilatation of renal pelvis and calyces with accompanying parenchymal atrophy or thinning
- Approximately 20 % of antenatally diagnosed hydronephroses are not found on postnatal ultrasound.
- PUJ obstruction is known to be associated with other types of congenital abnormality. This is seen in almost 50 % of patients.
- PUJ obstruction is bilateral in about 10 % of patients (Figs. 3.16, 3.17 and 3.18).
- About 10 % of patients with PUJ obstruction have ipsilateral vesicoureteral reflux and to detect this, a voiding cystourethrogram should be part of the work-up of these patients.
- There are also reports of coexisting PUJ obstruction and uretero-vesical junction obstruction. In these cases, the uretero-vesical obstruction is usually mild and PUJ obstruction should be treated first.
- Duplication anomalies usually cause PUJ obstruction at the lower poles and the possibility of vesicoureteral reflux should be rolled out.
- Rarely, the PUJ may be so severe leading to massive dilation of the renal collecting system and these patients may present with a palpable flank mass. This however is a rare and unusual presentation of PUJ at present.
- PUJ obstruction is often associated with other congenital anomalies, including:
  - Anorectal malformations
  - Contralateral multicystic kidney
  - Congenital heart disease
  - VATER (vertebra, anus, trachea, esophageal, renal) syndrome
  - Esophageal atresia

The SFU Grading System for Hydronephrosis

- Grade 0:
  - No hydronephrosis, intact central renal complex seen on ultrasonography
- Grade 1:
  - Only renal pelvis visualized, dilated pelvis on ultrasonography, no caliectasis
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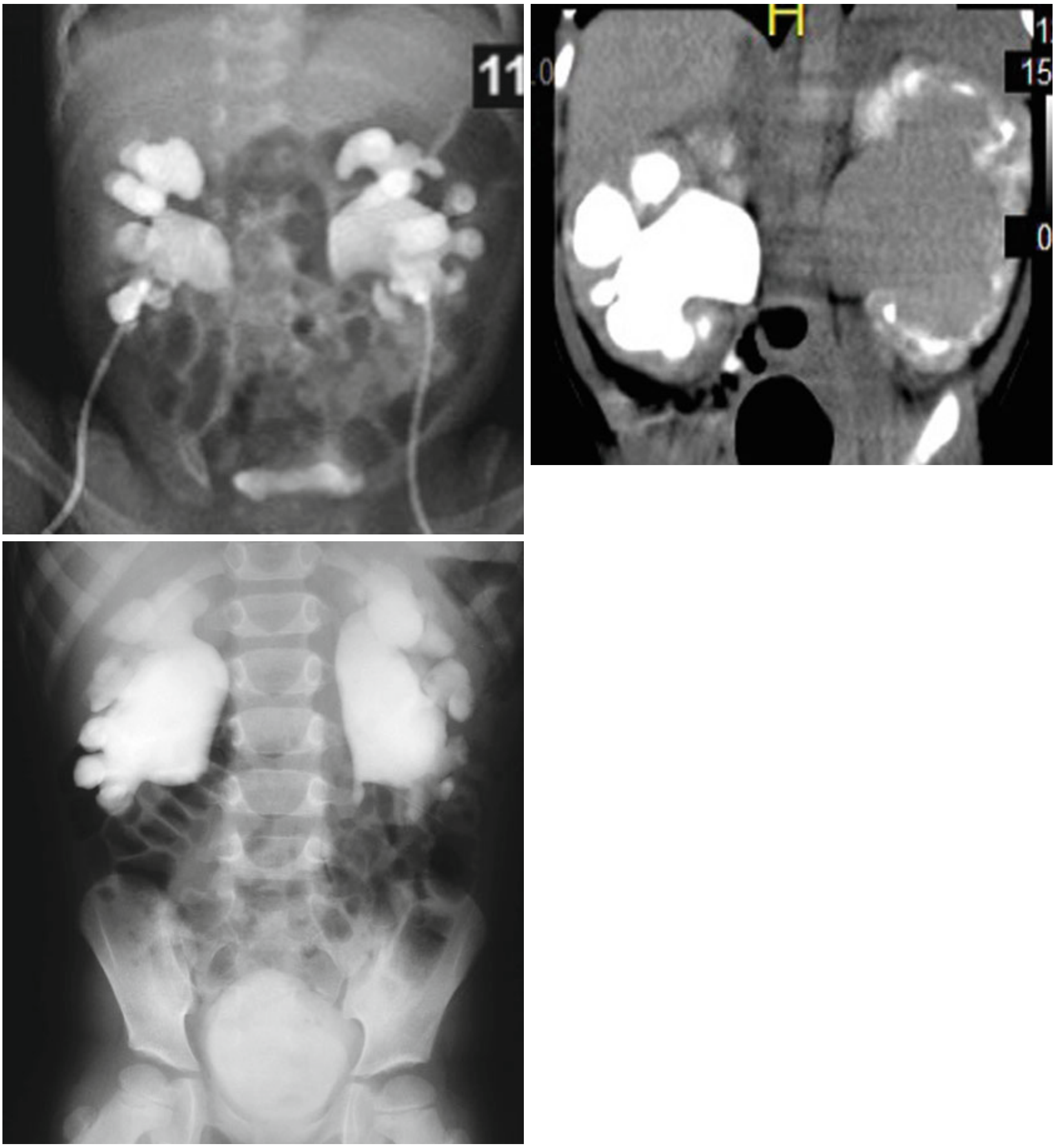
  - Moderately dilated renal pelvis and a few calyces
- Grade 3:
  - Hydronephrosis with nearly all calyces seen, large renal pelvis without parenchymal thinning
- Grade 4:
  - Severe dilatation of renal pelvis and calyces with accompanying parenchymal atrophy or thinning

3.6 Diagnosis and Investigations

- Prenatal evaluation:
  - Prenatal ultrasound is widely used to diagnose fetal abnormalities.
  - Among these abnormalities is PUJ obstruction.
  - Prenatal ultrasound evaluation should include the followings:
    - Amniotic fluid volume to rule out oligohydramnios
    - Bladder volume
    - Kidney size
    - Anteroposterior diameter of the renal pelvis
    - Other associated abnormalities
  - Functionally significant hydronephrosis can be determined when:
    - The anteroposterior diameter of the renal pelvis is more than 10 mm.
    - The ratio of the renal pelvis to the anteroposterior kidney size is more than 0.3.
    - There is evidence of caliectasis after 24 weeks of gestation.



Figs. 3.16, 3.17, and 3.18 Abdominal CT-scan and intravenous urography showing bilateral hydronephrosis secondary to PUJ obstruction

- Patients with PUJ obstruction diagnosed by prenatal ultrasound should have a postnatal ultrasound. The timing of ultrasound is variable and depends on the severity of the PUJ obstruction.
- In general, however, ultrasound examination should be avoided in the first 2 days after birth, because hydronephrosis may not be detected because of extracellular fluid shifts that will underestimate the degree of hydronephrosis.
- Therefore, in unilateral disease, ultrasonography should be performed at least after 48 h of life.
- These patients should also be placed on prophylactic antibiotics (amoxicillin 15 mg/kg) to prevent urinary tract infections.
- Other investigations include:
  - Complete blood count

  - Urine analysis and culture
  - Serum electrolytes, BUN and creatinine
  - Plain abdominal radiograph
  - Abdominal ultrasound
  - Abdominal CT-scan
  - Abdominal MRI
  - A nuclear renal scan can
  - Intravenous urography
  - Voiding cystourethrography
  - Percutaneous nephrostography
  - Cystoscopy and retrograde pyelography
  - A Whitaker antegrade pressure-flow study
- Serum electrolytes, BUN and creatinine are important to measure renal function especially in those with bilateral disease.
- Urine analysis and culture are important to roll out associated urinary tract infection especially in asymptomatic patients.
- Abdominal radiograph (Fig. 3.19):
  - A plain abdominal x-ray may show a soft tissue density secondary to a hydronephrotic kidney.
  - A plain abdominal x-ray may also show radiopaque stones complicating PUJ obstruction.
- Abdominal ultrasound (Figs. 3.20 and 3.21):
  - Renal ultrasound will show a dilated renal pelvis with a collapsed non-dilated ureter.
  - Renal ultrasound is also important to measure the size of the renal pelvis and it is useful for follow-p to monitor changes in the size of the renal pelvis.
  - Ultrasound can also help determine the size of the kidney, the size of renal and the thickness of renal parenchyma.
  - Ultrasound is also important to detect other associated urological abnormalities.
  - Duplex Doppler ultrasonography can be used to assess intrarenal vasculature and determine the resistive index.
    - Normal kidneys reliably demonstrate resistive indices less than 0.7, and obstructed kidneys show higher values.
    - This is especially reliable in the preoperative diagnosis of aberrant-accessory blood vessels associated with PUJ obstruction.
  - Renal ultrasound is a relatively cheap investigation, devoid of radiation and can easily be repeated.
- Intravenous urography (Figs. 3.22, 3.23 and 3.24):
  - Historically, intravenous pyelography (IVU) was used to evaluate patients with possible PUJ obstruction.
  - The administration of frusemide helps exclude a ‘baggy pelvis’.
  - Currently, intravenous urography is replaced by other less invasive and more informative investigations.
  - Intravenous urography has the risk of radiation exposure and contrast media including nephrotoxicity and anaphylactic reactions.
- The diagnosis of intermittent UPJ obstruction is confirmed if hydronephrosis is present when the child is symptomatic, and resolves when the child is well. A diuretic renal scan will document baseline renal function and may also provoke symptoms during the diuretic phase of the study, which confirms the diagnosis.

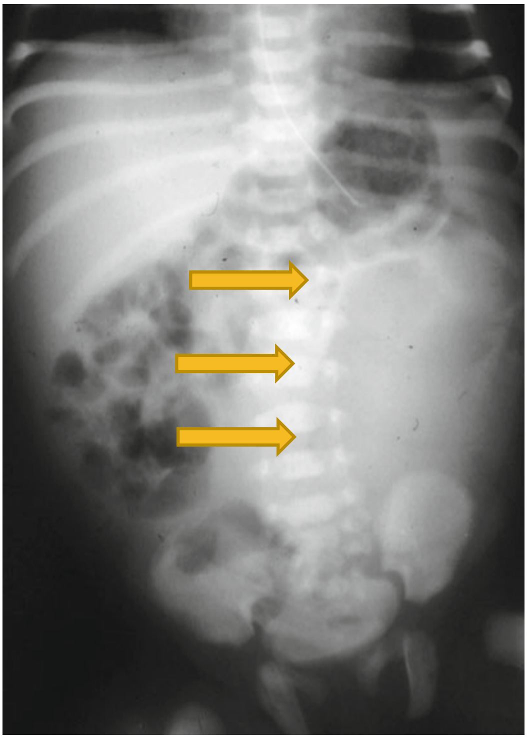
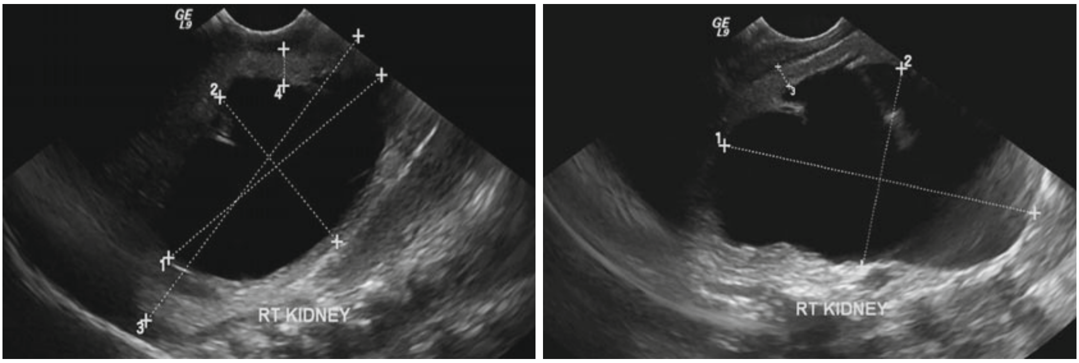
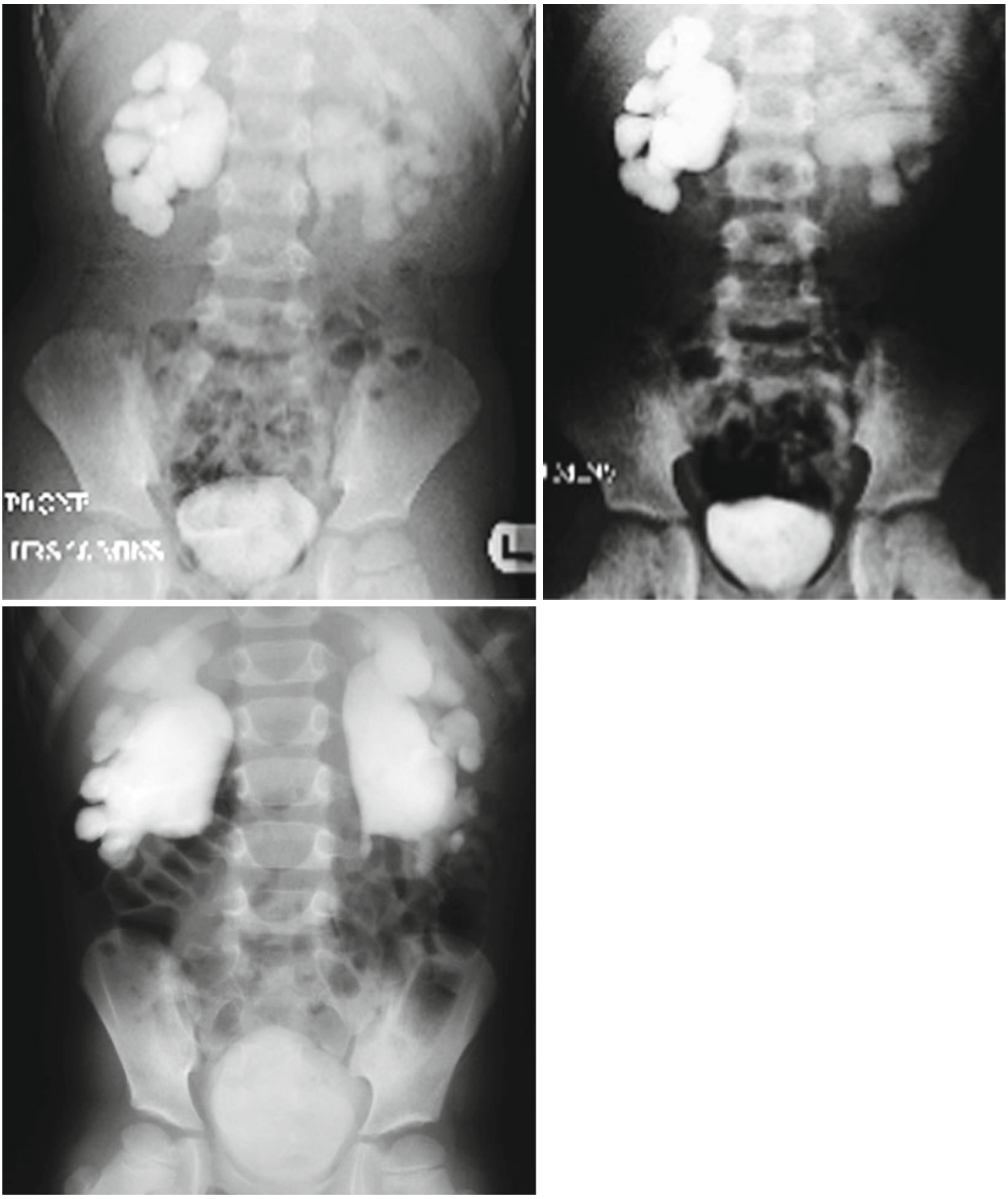


Fig. 3.19 Abdominal radiograph showing a soft tissue density on the left side in a child with severe left PUJ obstruction



Figs. 3.20 and 3.21 Andominal ultrasound showing severe hydronephrosis secndary to PUJ obstruction

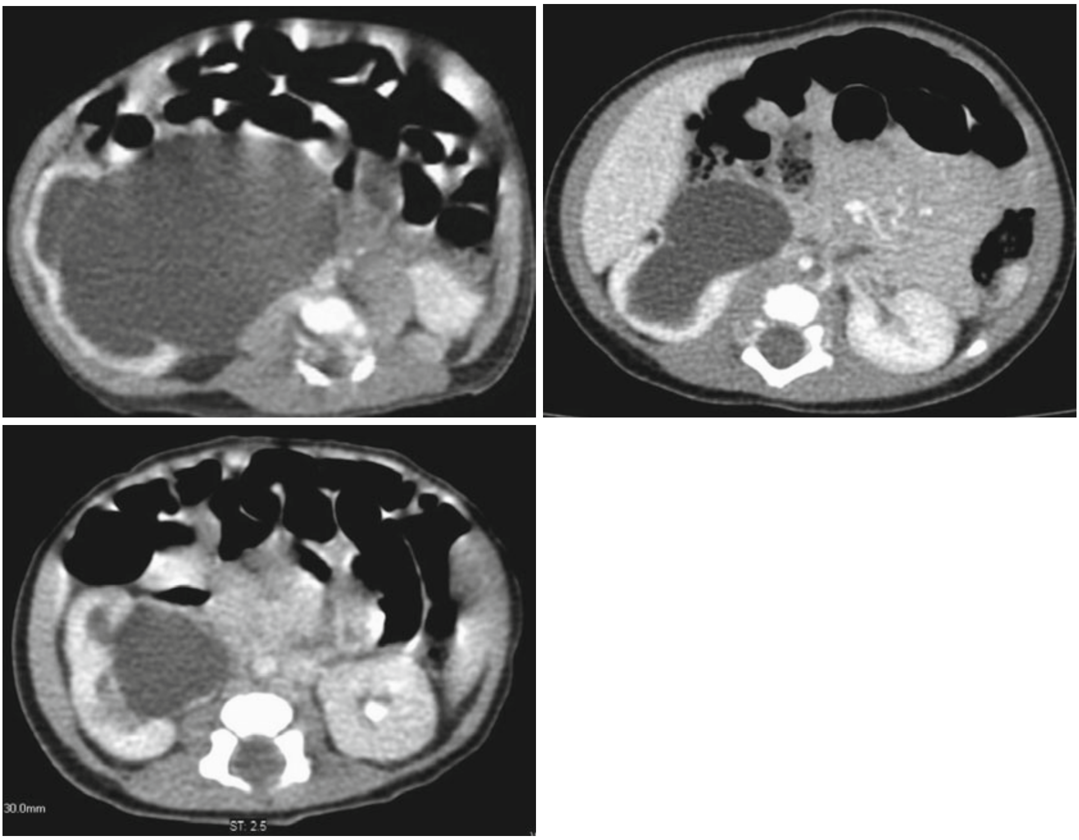
- Abdominal CT-scan (Figs. 3.25, 3.26, 3.27, 3.28 and 3.29):
  - – Abdominal CT-urography is very useful in establishing the severity of PUJ obstruction including the renal parenchymal volume.
  - – Establishing the anatomy of PUJ obstruction.
  - – Identification of an intrinsic cause or high-insertion PUJ.
  - – Demonstrating crossing vessels and their relationship to the ureter of the PUJ.
  - – The localization of these vessels and their possible contribution to renal obstruction is important for surgical planning and the most effective treatment modality.
  - – If an endopyelotomy is planned, this information can guide the surgeon in directing the endopyelotomy incision away from crossing vessels.
  - – It is also useful in outlining the location of secondary causes of PUJ obstruction including aberrant vessels, kinks, and adhesions.
  - – Spiral (helical) CT-scan is more useful as it provides superior longitudinal resolution.
  - – Abdominal CT-scan requires sedation or general anesthesia in very small children and also carries the risk of radiation exposure.
  - – Abdominal CT-scan has a sensitivity of 97 %, specificity of 92 %, and accuracy of 96 % in detecting crossing vessels associated with PUJ obstruction.
- Abdominal MRI (Figs. 3.30 and 3.31):
  - – Dynamic contrast-enhanced magnetic resonance urography (MRU) is the latest imaging modality used in assessing PUJ obstruction.
  - – In children, this study has several advantages:
    - No radiation exposure.
    - Excellent anatomical and functional details.
    - It provides details of renal vasculature, renal pelvis anatomy, location of crossing vessels, renal cortical thickness and scarring.
  - – The disadvantage of this investigation is that it is not readily available and require general anesthesia.
  - – Contrast-enhanced magnetic resonance angiography (MRA) was reported to have a sensitivity of 85 %, a specificity of 80 %, and a positive predictive value of 0.8 for the diagnosis of aberrant and obstructing renal arteries.
- Diuretic renography (Fig. 3.32):
  - – A diuretic renal scan should be performed to quantify relative renal function and to define the extent of obstruction.
  - – There are several isotope tracers that are used for diuretic renography including:
    - Mercaptotriglycylglycine (MAG-3)
    - Diethylenetriamine (DTPA)
    - Dimercaptosuccinic acid (DMSA)
    - Technetium-99m-mercaptoacetyltriglycine (^{99m} Tc-MAG3)
  - – This is the most noninvasive technique used to determine the severity and functional significance of PUJ obstruction.
  - – The preferred radioisotope is technetium-99m-mercaptoacetyltriglycine (^{99m} Tc-MAG3), which is taken up by the renal cortex, filtered across the glomerular basement mem-



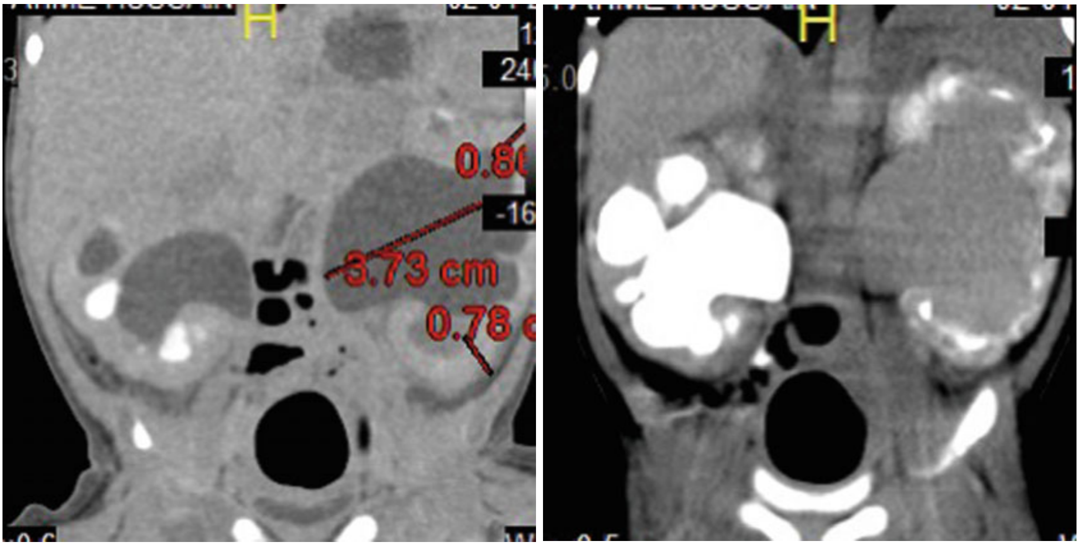
Figs. 3.22, 3.23, and 3.24 Intravenous urography showing bilateral PUJ obstruction

brane to the renal tubules, and excreted into the renal pelvis and urinary tract.

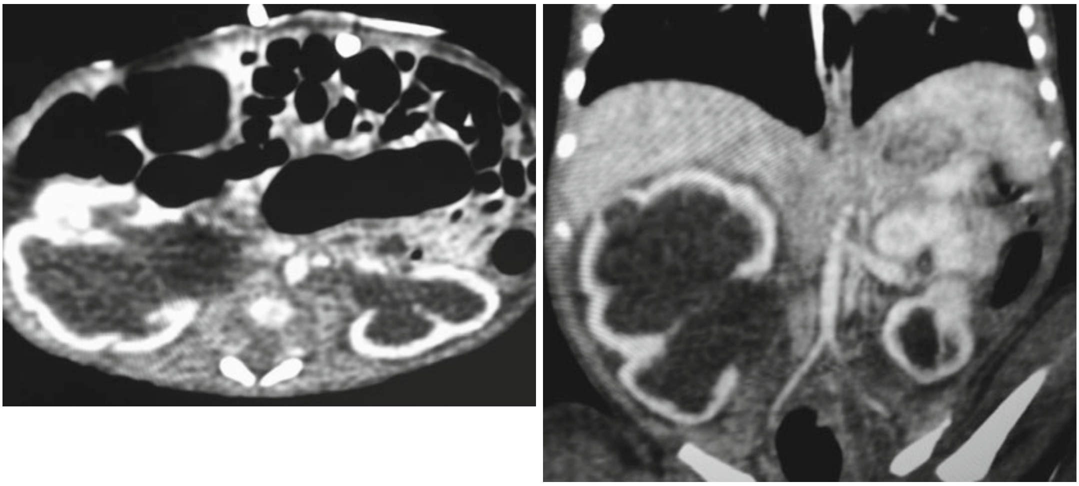
- MAG3 is another tracer that is mainly intravascular and secreted by proximal renal tubules, with a small fraction being filtered by the glomeruli.
- Another widely used tracer is technetium 99m diethylenetriamine penta-acetic acid (^{99m} Tc-DTPA), which, owing to the small size of molecule, diffuses within both intravascular and extravascular spaces, resulting in significant background activity.
- The diuretic renography measures the drainage time from the renal pelvis (referred to as washout) and assesses total and each individual kidney's renal function.



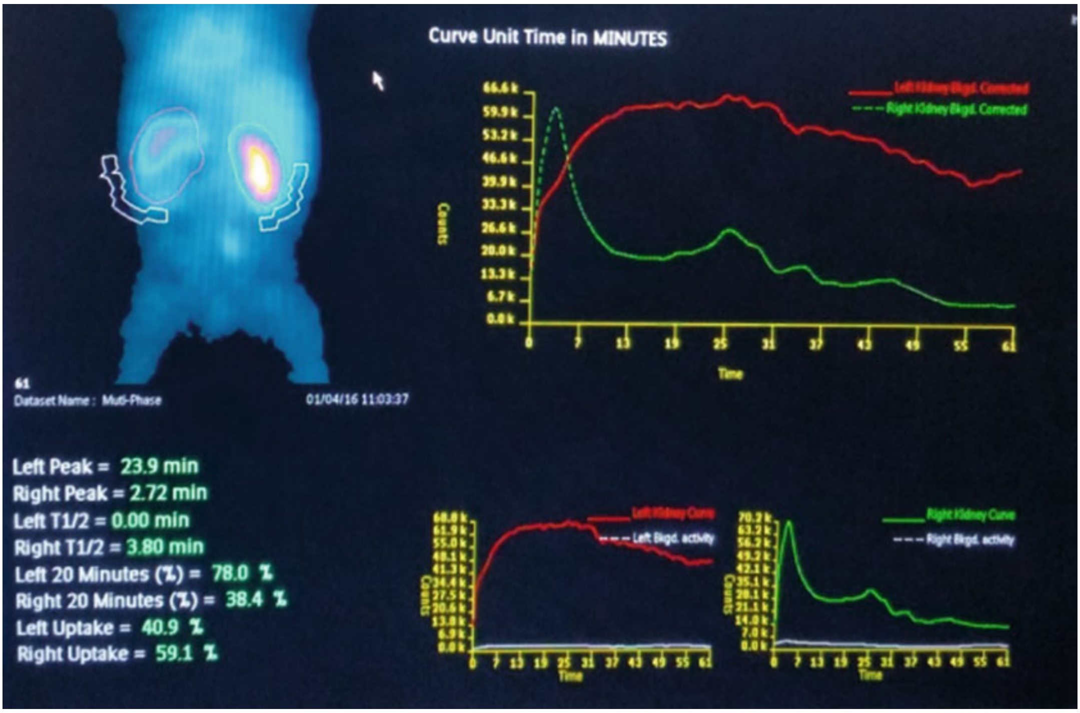
Figs. 3.25, 3.26, and 3.27 Abdominal CT-scans showing hydronephrosis secondary to PUJ obstruction (Note the very severe obstruction in the middle picture with almost complete renal atrophy where there is only a small rim of renal parenchyma remaining while in the lower one the renal parenchyma is still preserved)



Figs. 3.28 and 3.29 Abdominal CT-scan showing bilateral hydronephrosis secondary to PUJ obstruction



Figs. 3.30 and 3.31 Abdominal MRI showing bilateral hydronephrosis secondary to PUJ obstruction (Note the thickness of the renal parenchyma on the right side. It is thinned out as a result of severe obstruction and back pressure)


Curve Unit Time in MINUTES
Left Kidney Bkgd. Corrected
Right Kidney Bkgd. Corrected
Counts
66.6 k
59.9 k
53.2 k
46.6 k
39.9 k
33.3 k
26.6 k
20.0 k
13.3 k
6.7 k
0.0 k
0
7
13
19
25
31
37
43
49
55
61
Time
61
Dataset Name : Muti-Phase
01/04/16 11:03:37
Left Kidney Curve
Left Bkgd. activity
Right Kidney Curve
Right Bkgd. activity
Counts
Time

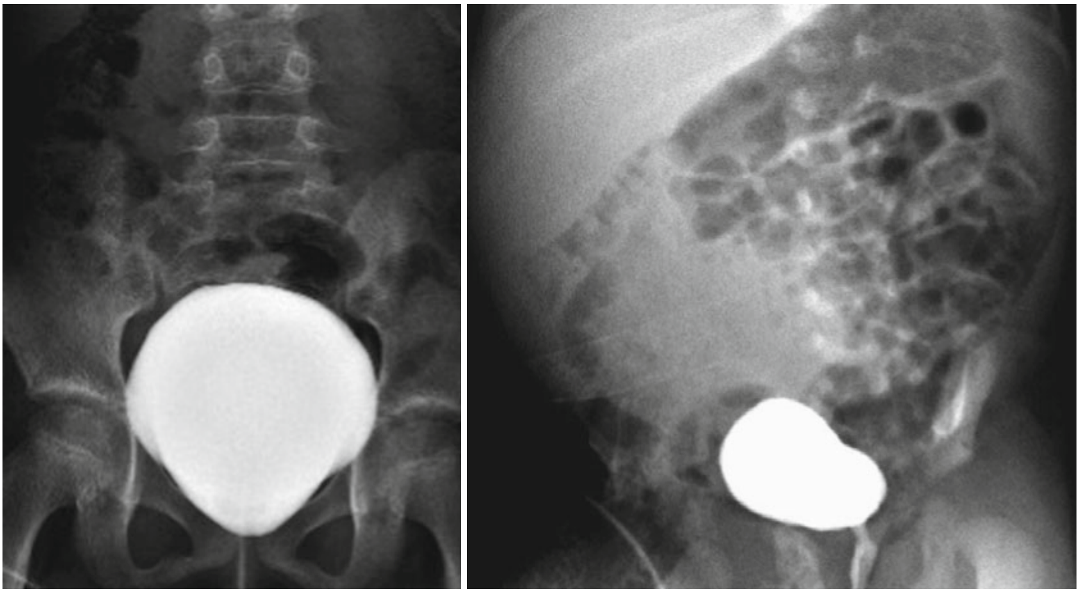
```
Left Peak =  23.9 min
Right Peak = 2.72 min
Left T1/2 = 0.00 min
Right T1/2 = 3.80 min
Left 20 Minutes (%) =  78.0 %
Right 20 Minutes (%) =  38.4 %
Left Uptake =  40.9 %
Right Uptake =  59.1 %
```

Fig. 3.32 A diuretic nephrogram of a child with a left PUJ obstruction

– The washout measurement correlates with the degree of obstruction.

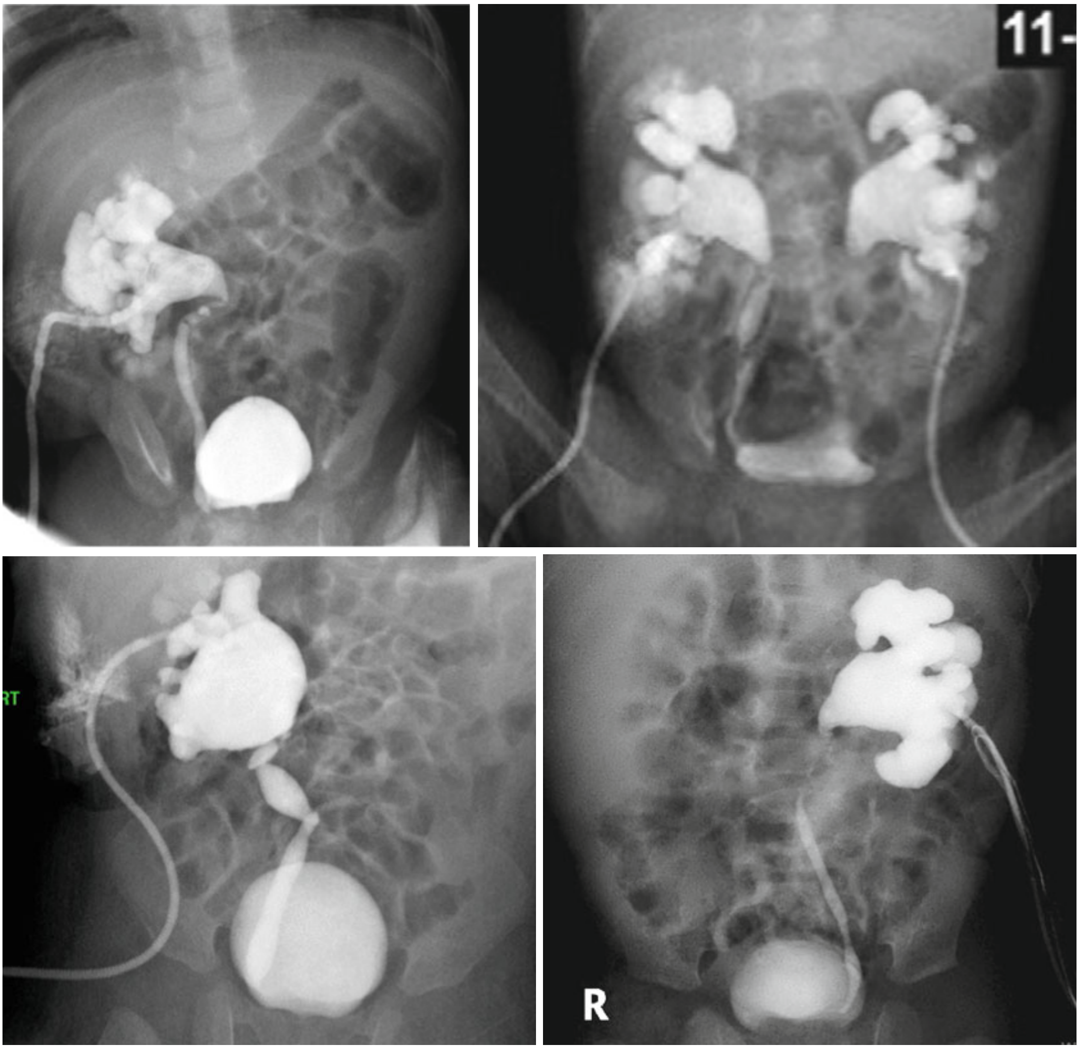
– The patency of the PUJ is determined by measuring the T1/2 (the time required for 50% of the isotope to be excreted) on the wash-out curve. Rapid drainage (low T1/2) indicates no obstruction, while impaired drainage or slow or no washout (T1/2 >20 min) indicates obstruction.

– Another important measurements in diuretic renography is the estimate of differential renal function. This is considered



Figs. 3.33 and 3.34 Voiding cystourethrograms in two children with PUJ obstruction (Note the absence of VUR. Note also the soft tissue density on the right side in the lower picture representing the enlarged right kidney)

  significant when it is less than 40 %. Diuretic (Furosemide) Renogram is performed to differentiate obstructive from nonobstructive hydronephrosis.
  - Sometimes an unusually high differential renal function can be seen on the affected kidney. This is attributed to an increase in single-nephron filtration or nephron volume.
  - Currently, a diuretic renal scan is important to diagnose those with functionally significant PUJ obstruction. The Reno graphic criteria include:
    - A flat or rising washout curve after diuretic with T 1/2 of greater than 20 min and differential function of less than 40.
    - The differential function is important in determining the need for intervention, especially in asymptomatic patients, and in selecting the appropriate treatment (pyeloplasty vs nephrectomy).
    - Poorly functioning kidneys (<10 %) are often best treated with nephrectomy.
  - In general, a half-life greater than 20 min to clear the isotope from the kidney is considered indicative of obstruction, although other urologists use split function, comparing the function of the two kidneys, as a means to identify patients for surgery.
  - Renal isotope scan is also used to assess outcomes after surgical correction of PUJ obstruction.
- A voiding cystourethrography (VCUG) (Figs. 3.33 and 3.34):
  - A voiding cystourethrography (VCUG) is part of the work up of these patients.
  - This is to rule out vesicoureteral reflux.
  - Vesicoureteral reflux (VUR) has been found in as many as 40 % of children with PUJ obstruction but the reported incidence of VUR in association with PUJ obstruction is about 10 %.
  - The VUR is usually mild and usually resolve spontaneously.
- Retrograde/antegrade pyelography:
  - Retrograde pyelography was used to assess the upper ureter and renal pelvis.
  - Retrograde or antegrade pyelography requires general anesthesia.
  - It is now mostly performed at the time of surgical correction of the PUJ obstruction to establish the exact site of obstruction.
  - A percutaneous nephrograohy (Figs. 3.35, 3.36, 3.37 and 3.38):



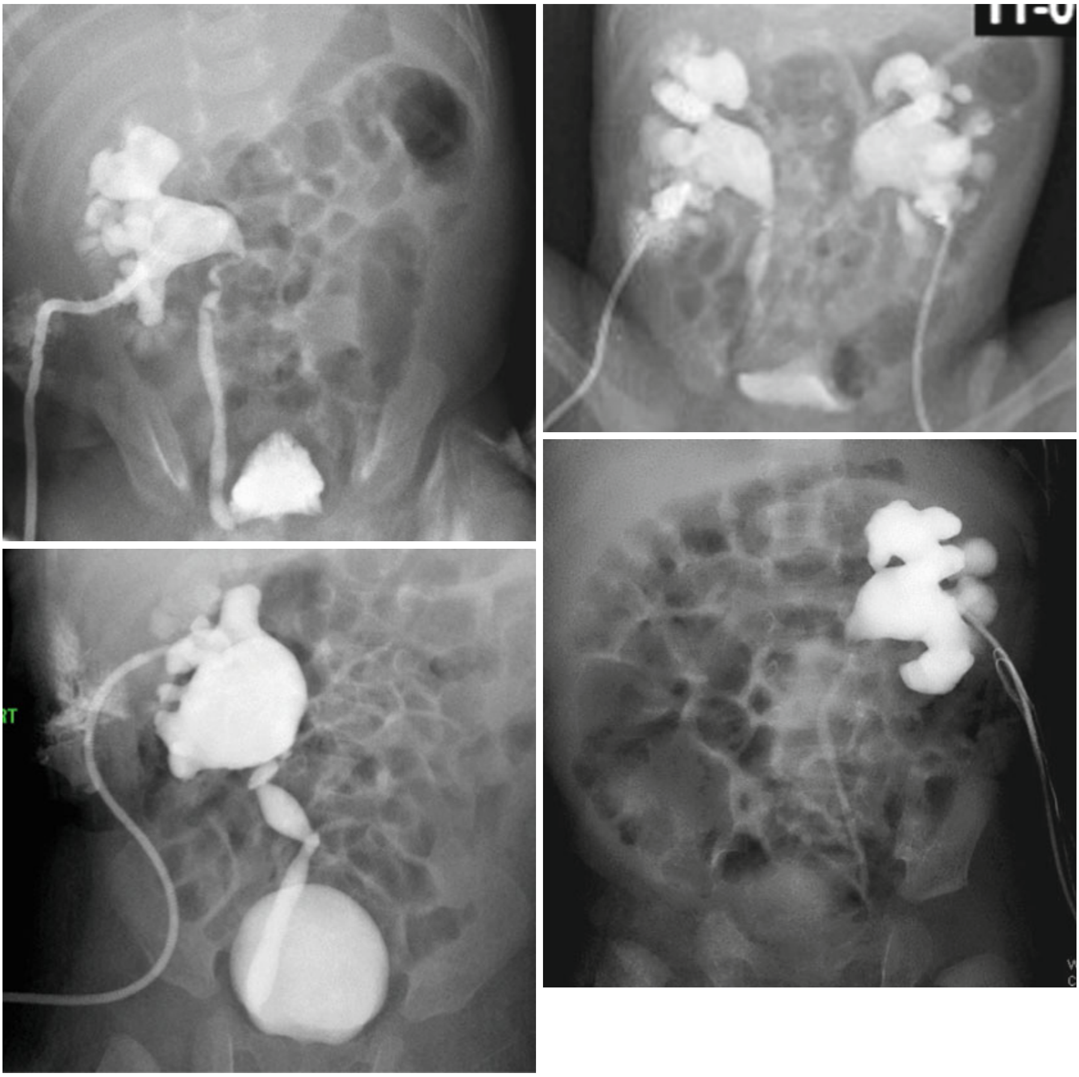
Figs. 3.35, 3.36, 3.37, 3.38, and 3.39 Nephrostograms showing unilateral and bilateral PUJ obstructions. Percutaneous nephrostograms are useful especially in newborns with severe hydronephrosis (Note only they confirm the diagnosis and severity of PUJ but they are useful for temporary drainage of the obstructed kidney to refive the pressure from the renal parenchyma)

  - This can be diagnostic and also used to temporary drain the kidney to decompress the renal pelvis and relive the pressure on the renal parenchyma.
  - This is valuable especially in newborns with severe obstruction. The ureter is small in these patients which makes it difficult to reconstruct the PUJ and a temporary nephrostomy will drain the obstructing kidney and buy time.
- Pressure flow studies:
  – When the radiological investigations are equivocal, a Whitaker antegrade pressure-flow study may be performed to further evaluate for PUJ obstruction.
  – This is done as follows:
    - A small-diameter nephrostomy tube is inserted percutaneously into the kidney.
    - Dilute contrast medium is instilled, and the intrarenal collecting system is pressure-monitored.

  - Under fluoroscopy, the PUJ is assessed and drainage through this segment is evaluated.
  - High intrarenal pressures is indicative of PUJ obstruction.
  - Low intrarenal pressures in the presence of hydronephrosis are consistent with normal variance.
  - The Whitaker test is a pressure flow study that has proven useful in equivocal PUJ obstruction in children.
  - A catheter is introduced percutaneously into the renal pelvis. The patency of the PUJ is challenged fluid infusion via the catheter and simultaneously measuring the intrapelvic pressure.

3.7 Management of Newborns with PUJ Obstruction

- The timing of surgical correction of PUJ obstruction in newborns is highly controversial.
- Immediate surgery is not necessary for those newborns with relatively preserved differential renal function (>40 % of differential renal function).
- These patients can be observed safely nonoperatively as in some of them the obstruction will resolve spontaneously.
- These patients should be covered with antibiotic prophylaxis.
  - The use of antibiotic prophylaxis in mild hydronephrosis is still controversial.
  - Most authors advocate antibiotic prophylaxis for those with moderate-to-severe hydronephrosis (SFU grade 3 or 4).
- Urinary tract infection in these patients increases the chance of fibrosis and parenchymal damage.
- Patients with renal function >40 % are monitored with repeat renal scans at 3- to 6-month and 12-month intervals, and surgery is performed only if a clear deterioration in renal function is present.
- In cases in which the differential function is <10 %, some recommend the insertion of a nephrostomy tube to determine whether return of function will be sufficient.
- Others consider this a non-functioning kidney and there is no point in inserting a nephrostomy. Add to this the fact that nephrostomy is difficult to maintain in infants and children and it is known to be associated with bacteriuria.
- Nephrectomy is indicated in those with a differential function <10 % and complicated by hypertension or recurrent urinary tract infection.
- Surgical Therapy:
  - Prolonged partial PUJ obstruction is deleterious to the newborn kidney and can be reversed by early relief of the obstruction.
  - Spontaneous resolution of hydronephrosis although well known, 15–33 % of patients with asymptomatic neonatal hydronephrosis show progressive ipsilateral renal deterioration, and about one half of them never regain the lost function by pyeloplasty.
  - There is a definite percentage of patients with PUJ obstruction treated conservatively who will sustain irreversible renal damage that could have been prevented by early pyeloplasty.
- Indications for surgical interventions in PUJ obstruction:
  - Unilateral PUJ obstruction with less than 40 % of differential renal function on diuretic renograms.
  - Bilateral severe PUJ obstruction with renal parenchymal atrophy.
  - Obstructive pattern on diuretic renograms with abdominal mass, urosepsis, or other symptoms.
  - Recurrent UTI under antibiotic prophylaxis.
- A temporary percutaneous nephrostomy was advocated in newborns with severe hydronephrosis. The aims of this include (Figs. 3.40, 3.41, 3.42 and 3.43):
  - To confirm the diagnosis and document the severity of obstruction.
  - To drain the obstructed kidney and relive the pressure on the renal parenchyma.
  - Newborns and because of the partial PUJ obstruction have a small size ureter that



Figs. 3.40, 3.41, 3.42, and 3.43 Percutaneous nephrostograms showing unilateral and bilateral PUJ obstruction in newborns and infants (Note the degree of obstruction and the extent of hydronephrosis. The nephrostomy is also useful for temporary drainage of the obstructed kidney)

  makes it difficult operatively to reconstruct the new PUJ and placing a temporary nephrostomy will time to decompress the kidney, increase the size of the ureter and allow the child to grow.
  - Nephrostomy tubes are also known to be associated with complications including sepsis, kinking and spontaneous dislodgment.

3.8 Treatment

- The aims of treating patients with PUJ obstruction are:
  - Relive the obstruction
  - Improve renal drainage
  - Maintain or improve the renal function
- There is no evidence that prenatal intervention in infants with either a single obstructed

  kidney or bilateral involvement improves renal outcome.
- Antenatal intervention however is recommended in those with extremely severe PUJ obstruction and only be done in centers with experienced surgeons as this may be associated with morbidity and fetal mortality.
- Asymptomatic patients with PUJ obstruction:
  - The ultimate goal of management is to preserve renal function and avoid unnecessary surgery.
  - Managing asymptomatic patients is challenging, because the natural course of PUJ obstruction is variable.
  - It appears that many patients with PUJ obstruction will have stable renal function and improvement in the degree of hydronephrosis during long periods of observation.
  - However, others will have deterioration of their renal function, and appear to benefit from surgical repair of PUJ obstruction.
  - There is no reliable method to predict which patients with asymptomatic PUJ obstruction, their kidney function will deteriorated and whether the function of a kidney with PUJ obstruction will remain unaffected during the period of observation.
  - As a result of this, there is controversy on the role of watchful observation with surgical intervention only in those who develop symptoms or if there is a decrease in renal function. This approach may prevent unnecessary surgery in some asymptomatic patients with PUJ obstruction.
  - Patients with PUJ obstruction are monitored closely with renal ultrasonography and nuclear scans every 3–4 months.
  - It is important to monitor the renal pelvic dilatation with serial ultrasounds. This is important to assess:
    - Changes in renal pelvic dilatation
    - Renal parenchymal thickness
    - The presence of scarring, and function.
  - Patients with asymptomatic PUJ obstruction should be monitored and followed-up with serial renal ultrasounds to detect any change in the degree of hydronephrosis that may necessitate surgical intervention.
    - Renal ultrasound evaluations are performed every 3–4 months until the child reaches 1 year of age, every 6 months for the next 2 years, and then annually.
    - If the renal ultrasound shows increasing hydronephrosis, a diuretic renogram is repeated to detect any change in renal function or confirm that the renal function is stable.
    - If diuretic renogram shows deterioration of >10 % in the renal function on the affected side, or the relative renal function is <40 %, surgery is recommended.
    - These studies are performed more frequently (every 2–3 months) if the relative renal function is borderline, and significant hydronephrosis is present.
  - The problem is more complicated in those with bilateral asymptomatic PUJ obstruction as the relative renal function may not be a reliable measure.
  - In these patients, glomerular filtration rate can be measured with serum creatinine and/or by renal scan. If renal function is significantly decreased, surgery is indicated to relieve PUJ obstruction.
  - Antibiotic prophylaxis:
    - This has been recommended in these patients because urinary stasis is believed to be a risk factor for urinary tract infection.
    - This is also controversial and does not appear that it is beneficial in children with PUJ obstruction especially those with mild PUJ obstruction.
    - There are those who advocate giving antibiotic prophylaxis for patients with severe, grade IV hydronephrosis until the time of the voiding cystourethrogram (VCUG). If the VCUG does not show vesicoureteral reflux, the prophylactic antibiotics are discontinued.
    - Others will give prophylaxis antibiotics for all patients with PUJ obstruction.

- Children with PUJ obstruction who are symptomatic require operative intervention.
- Kidney stones sometimes develop in those with PUJ obstruction and these patients should be treated with open pyelolithotomy and pyeloplasty.
- Patients with PUJ obstruction who present with acute pyelonephritis are treated first with antibiotics. Surgical repair is performed when the infection has resolved but if pyelonephritis does not respond to antibiotics, a temporary percutaneous nephrostomy should be placed to drain the kidney and relieve the obstruction.
- Initially, most children with incomplete PUJ obstruction are treated conservatively and monitored closely.
- Monitoring of these patients include serial renal ultrasonography and renal isotope scan.
- Surgical intervention is indicated in patients with PUJ obstruction:
  - Who are symptomatic (pain, hypertension, hematuria, secondary renal calculi, and recurrent urinary tract infections).
  - With significantly impaired renal drainage or poor renal growth
  - With deterioration of renal function (a serial loss in renal function >10 %).
  - With clearance half-time (T 1/2) greater than 20 min, differential function less than 40 %, and ongoing parenchymal thinning with or without contralateral compensatory hypertrophy.
  - With progressive increase in the size of renal pelvis on serial imaging.
  - With bilateral PUJ obstruction and thinning of renal parenchyma.
- There are several methods to treat PUJ obstruction.
- Open surgical Therapy (Fig. 3.44):

Asymptomatic Patients with PUJ Obstruction

- Observation is appropriate for asymptomatic patients with PUJ obstruction and hydronephrosis that is mild to moderate in severity (i.e. Society of Fetal Urology [SFU] grade II to III).
- These patients are followed-up with ultrasound examination every 4 (Grade III) to 6 (Grade II) months in the first year of life, then every 12–18 months thereafter.
- If there is an increase in the degree of hydronephrosis, a diuretic renogram is performed.
- If the affected kidney has <40 % of split renal function, or there is a serial loss

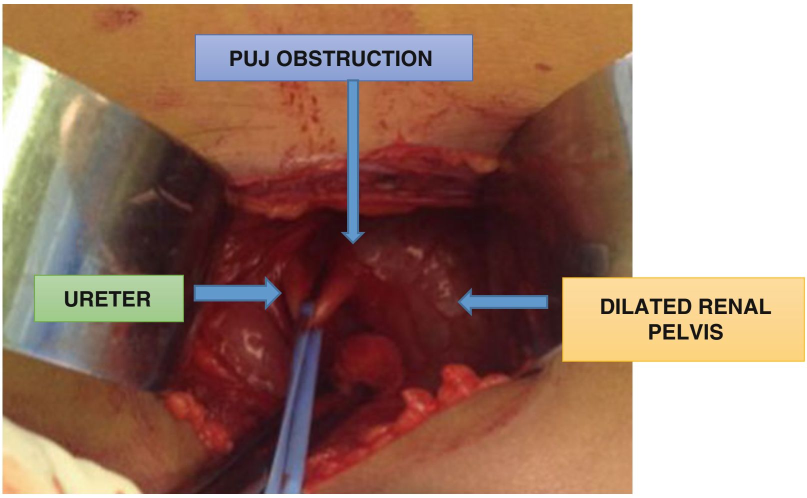


Fig. 3.44 An intraoperative photograph showing hydronephrosis secondary to PUJ

>10 % from a previous study, surgical intervention is recommended.

- Newborns who have persistent SFU grade IV hydronephrosis require closer observation and frequent renal ultrasound follow-up.
- In these patients, a diuretic renogram is performed at 6–8 weeks of age.
  - If the hydronephrotic kidney has decreased renal function (<40 % of split renal function) compared with its normal contralateral side, surgical intervention is recommended.
  - If the hydronephrotic kidney have equal function compared with the normal contralateral kidney, the renal sonogram is repeated in 4–6 weeks. If the sonogram shows improvement, these patients are followed-up with serial renal ultrasounds at 3–4 month intervals.
  - Any worsening of the hydronephrosis calls for a diuretic renogram.
  - If these serial sonograms show continued SFU grade IV hydronephrosis without substantial change from previous studies:
    - Continued observation and monitoring including renal ultrasound and diuretic renograms
    - If the family prefer, surgical intervention is recommended.

- In 1936, Foley introduced the YV-plasty for the correction of PUJ obstruction.
- Culp and DeWeerd designed a spiral flap in the dilated pelvis and used it to repair the defect of the PUJ.
- The Foley Y-V plasty is used to treat PUJ obstruction and those with the high-insertion variant but cannot be used in the presence of apparent lower-pole vessel.
- Spiral and vertical flaps (e.g. Culp and DeWeerd, Scardino and Prince) are useful for those with a long-strictured segment of the ureter. The proximal strictured ureter is re-tubularized using the redundant renal pelvis.
- In 1946, Anderson and Hynes described their operation to treat PUJ obstruction. The Anderson-Hynes dismembered pyeloplasty is currently the most commonly used procedure to repair PUJ obstruction.
- In children, the procedure of choice to treat PUJ obstruction is an Anderson-Hynes dismembered pyeloplasty.
- The Anderson-Hynes dismembered pyeloplasty is particularly useful for those with the high-insertion variant of PUJ obstruction.

Indications for Surgery in PUJ Obstruction

- Symptomatic patients (flank pain, urinary tract infection, and renal stones).
- Unilateral PUJ obstruction with <40 % of differential renal function on diuretic renograms or there is a serial loss in renal function >10 %.
- Bilateral severe PUJ obstruction with renal parenchymal atrophy.
- Obstructive pattern on diuretic renograms with abdominal mass, urosepsis, or other symptoms (e.g., cyclic flank pain, nausea, vomiting).
- Recurrent UTI in spite of antibiotic prophylaxis.
- Massive hydronephrosis (renal pelvis diameter >4–5 cm.
- Parental preference in those who require frequent observation and invasive testing.

Patients with renal function more than 40 % on the affected side are monitored with repeat renal scans at 3- to 6-month and 12-month intervals, and surgery is performed only if a clear deterioration in renal function is present.

Patients with Renal Differential Function <10 %

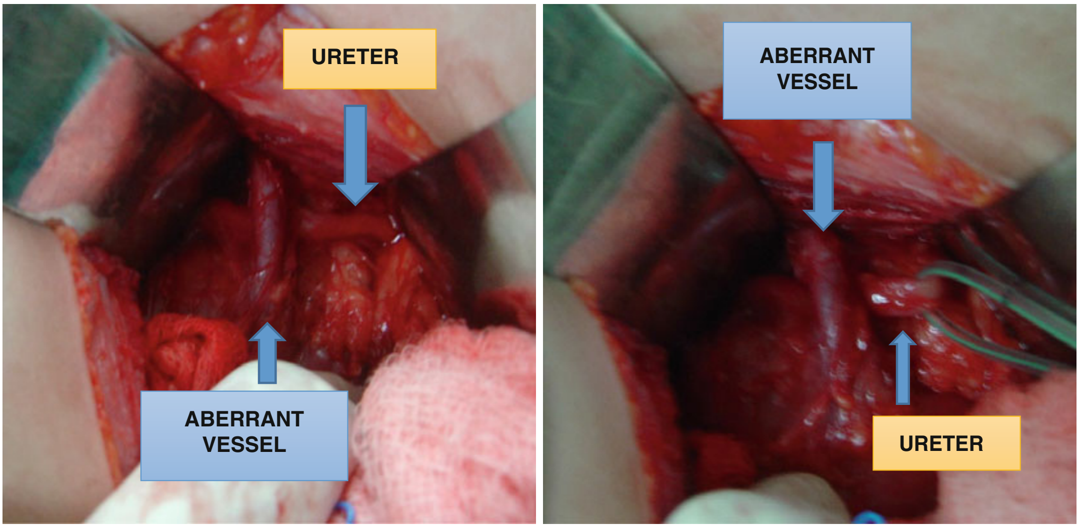
- Some recommend insertion of a nephrostomy tube to determine whether return of function will be sufficient.
- Others consider nephrectomy to relieve recurrent infection or renal hypertension.
- In the absence of significant hydronephrosis, some surgeons will observe these patients and will consider nephrectomy only if they develop hypertension or recurrent urinary tract infection.

  - In this technique, the obstructed segment is completely resected, the renal pelvis is tapered with reanastomosis of the renal pelvis and ureter in a dependent funneled fashion.
  - The decision of whether to use a ureteral stent transiently is still controversial.
  - Pyeloplasty can be performed through one of these approaches:
    - A flank, dorsal lumbotomy
    - An anterior extraperitoneal approach
    - Laparoscopic pyeloplasty
    - Robotic assisted pyeloplasty
  - The success rate of open Anderson-Hynes dismembered pyeloplasty for treating PUJ obstruction exceeds 95 %.
  - There are those who use ureteral stents routinely.
  - Others prefer using a double “J” stent.
  - The use of perianastomotic drain following the repair is also controversial.
  - The routine use of nephrostomy is also controversial.
  - While open pyeloplasty is still considered the standard treatment of UPJ obstruction in infants, laparoscopic pyeloplasty, with or without robotic assistance, is the treatment of choice in older children and in most adults.
- Laparoscopic pyeloplasty:
  - Traditionally, PUJ obstruction has been repaired with an open pyeloplasty.
  - Laparoscopic pyeloplasty was first introduced in adults in 1993 by Schuessler.
  - The success of laparoscopic pyeloplasty is comparable with those of open pyeloplasty, with success rates reported to be as high as 96–98 %.
  - Laparoscopic pyeloplasty is reported to be feasible and safe in children.
  - Currently, laparoscopic pyeloplasty is performed for older children.
  - It is technically unfeasible in very small children and infants because of space constraints.
  - Laparoscopic pyeloplasty is a technically demanding procedure that generally requires significant laparoscopic experience.
  - A small intrarenal pelvis is a relative contraindication to laparoscopic pyeloplasty.
  - Laparoscopic pyeloplasty being a minimally invasive technique has several advantages including:
    - Shorter hospital stay
    - Faster recovery
    - Decreased morbidity
    - Better cosmetic result
    - The success rates are comparable with those of open pyeloplasty
  - Laparoscopic pyeloplasty is divided according to the approach into two types:
    - Transperitoneal laparoscopic pyeloplasty
    - Retroperitoneoscopic laparoscopic pyeloplasty
  - Laparoscopic pyeloplasty can be offered to patients with:
    - Severe hydronephrosis
    - Aberrant crossing vessels
    - Long-segment PUJ strictures
    - Secondary PUJ obstruction

Surgical Treatment for PUJ Obstruction

- Open pyeloplasty
- Laparoscopic pyeloplasty
- Percutaneous endopyelotomy
- Retrograde endopyelotomy
- Endopyeloplasty
- Robotic-assisted laparoscopic pyeloplasty
- Percutaneous balloon dilatation
- Endoscopic balloon dilatation

    - PUJ obstruction and concomitant renal calculi
    - Anomalous and solitary kidneys.
    - Failed open pyeloplasty
  - The success rates of transperitoneal laparoscopic pyeloplasty and retroperitoneoscopic laparoscopic pyeloplasty are comparable (96.4 % versus 96.6 %).
  - A skill full laparoscopic surgeon is an important factor for this success rate.
  - Retroperitoneoscopic laparoscopic pyeloplasty takes more operative time when compared with transperitoneal laparoscopic pyeloplasty owing to the limits of working space and more difficult suturing.
  - Transperitoneal laparoscopic pyeloplasty on the other hand is known to be associated with:
    - A significantly greater postoperative pain
    - A higher requirements for analgesics
    - A higher rate of temporary ileus
    - A longer hospital stay
  - It is now recommended that open pyeloplasty is the procedure of choice in infants younger than 6 months. Laparoscopic pyeloplasty is reserved for older children and to be done by skillful laparoscopic surgeons.
- Robotic-assisted laparoscopic pyeloplasty:
  - Robotic-assisted laparoscopic pyeloplasty has become increasingly popular to treat PUJ obstruction.
  - The da Vinci robotic surgical system has been used successfully to treat PUJ obstruction.
  - Suturing the anastomosis in the PUJ is much easier when compared to the laparoscopic technique.
  - The results are similar to those of conventional laparoscopic pyeloplasty.
  - It is costly and collision of the robotic arms in small infants is another drawback.
- Single-port pyeloplasty:
  - In this technique, laparoscopic pyeloplasty is performed via a single port placed at the umbilicus.
  - This is technically challenging owing to instrument crowding, loss of triangulation, and difficult suturing.
  - One advantage of this technique is better cosmetic results.
- Endoscopic treatment of PUJ obstruction (Endopyelotomy):
  - This is an endoscopic incision of the PUJ.
  - The aim is to create a more funneled drainage system and to bring the PUJ more dependent or below the area of obstruction.
  - Endoscopic incision is performed through the obstructing segment of the PUJ.
  - This is performed either as:
    - An antegrade (percutaneous) endopyelotomy
    - A retrograde (endoscopic) endopyelotomy via a ureteroscope
  - In a percutaneous endopyelotomy, a small incision is made in the flank through which a scope is advanced through the kidney into the renal pelvis to incise the UPJ.
  - Ureteroscopic endopyelotomy involves passing a scope through the urethra, bladder and ureter to incise the PUJ.
  - The endopyelotomy incision is performed through the area of obstruction with:
    - A laser
    - An electrocautery
    - An endoscopic scalpel
  - The vascular anatomy at the PUJ is important during an endopyelotomy.
  - Most vessels associated with PUJ lie in the anteromedial plane but accessory vessels may lie posteriorly or laterally.
  - If an endoscopic incision is made in the posterior-lateral plane, intraoperative hemorrhage may occur.
  - The best recommendation is to make sure that all incisions in the ureteral narrowing are directed laterally to minimize the chance for damage to the lower pole vessel.
  - Prior to incising a PUJ obstruction, it is important to evaluate adjacent ureteral vasculature using either an intraluminal ultrasonography, CT-scan or MRA.
  - Endopyelotomy is contraindicated in the presence of a crossing posterior or lateral vessel (Figs. 3.45 and 3.46).



Figs. 3.45 and 3.46 Intraoperative photographs showing an aberrant vessel crossing and compressing the ureter leading to PUJ obstruction

  - The endoscopic incision should be performed full-thickness through the PUJ and into perirenal fat.
  - To ensure a proper adequate incision, extravasation of contrast should be seen on pyelography during the procedure.
  - Most surgeons dilate the newly incised area with a balloon catheter to help ensure a complete incision.
  - This is followed by prolonged ureteral stenting, for a period of 4–8 weeks. The stent help keeps the incised PUJ open and maintains renal drainage.
  - Endopyelotomy is a reasonable option in patients with mild-to-moderate hydronephrosis and reasonably good renal function.
  - The area of stricture should be short (<1.5 cm), and no crossing vessels should be defined on preoperative or intraoperative imaging.
  - Endopyelotomy is also particularly useful following a failed open or laparoscopic pyeloplasty.
  - The success rates with the percutaneous and ureteroscopic endopyelotomy are 80–90 %.
- Endopyeloplasty:
  - This was first reported in 2002 by Gill et al from the Cleveland clinic.
  - The procedure is performed through a percutaneous tract via a 26 F nephroscope.
  - It consists of horizontal suturing of a standard vertical endopyelotomy incision.
  - Indications for endopyeloplasty include:
    - A short-segment PUJ obstruction
    - Absence of crossing renal polar vessels
    - No prior surgery in the PUJ.
  - The results of endopyeloplasty are comparable to those of endopyelotomy.
- Ureterocalicostomy:
  - A partial nephrectomy is performed and the ureter is anastomosed to a lower-pole renal calyx.
  - This is usually reserved for patients following a failed open pyeloplasty when no extrarenal pelvis and significant hilar scarring are present.
- Balloon dilatations of PUJ obstruction (Figs. 3.47 and 3.48):
  - Balloon dilatation of PUJ obstruction was first done in 1982 by Kadir et al in 1982.
  - Balloon dilatation can be done antegrade, retrograde or combined and the success rate is variable.
  - Percutaneous or endoscopic balloon dilatation of PUJ is another alternative to treat PUJ obstruction in children.

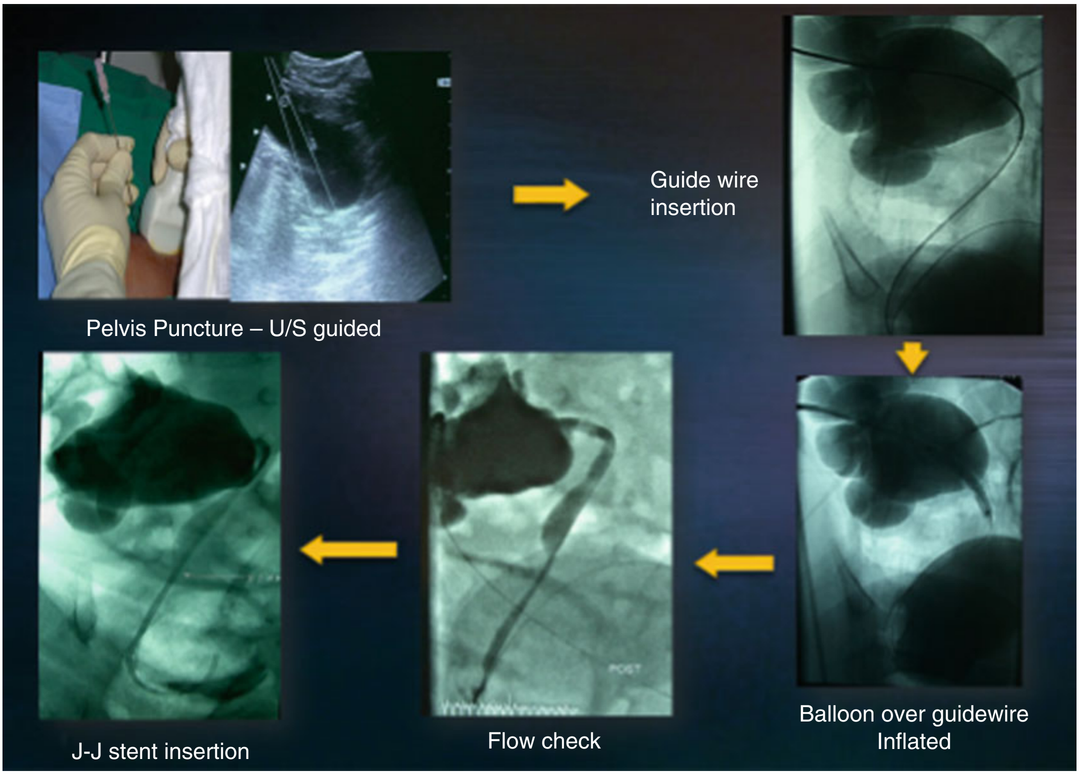

Guide wire
insertion
Pelvis Puncture – U/S guided
J-J stent insertion
Flow check
POST
Balloon over guidewire
Inflated

Fig. 3.47 Clinical and radiological pictures showing the steps of percutaneous balloon dilatation of PUJ obstruction. A double J-stent is left in place for 6–8 weeks

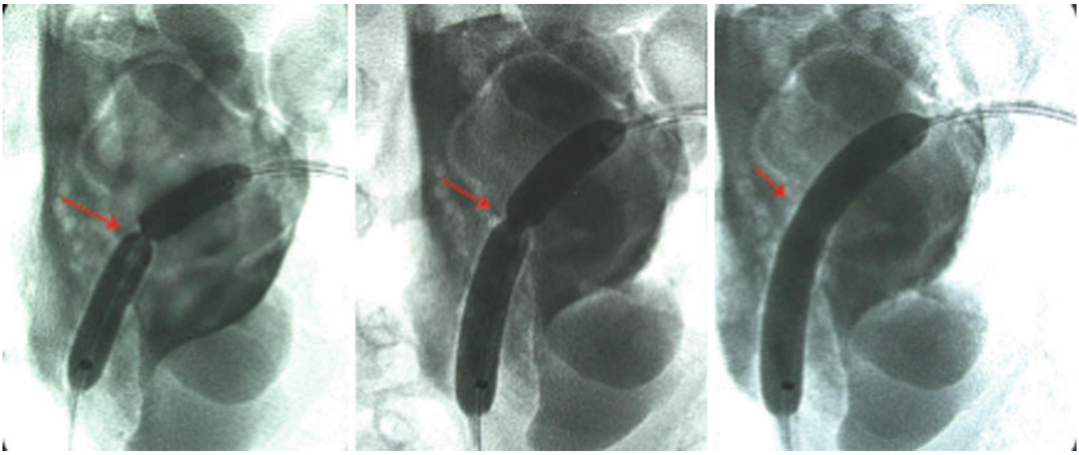


Fig. 3.48 Radiological photographs showing abolishing the wasting at the PUJ which is an important prognostic sign

- This is performed by interventional radiologist.
- The site of obstruction is defined and the stricture is dilated with balloon dilators.
- A double "J" stent is passed percutaneously and left in place to keep the dilated site patent.
- Balloon dilatations are most appropriate in pediatric populations because they are

the least invasive approach and are associated with the lowest risk of hemorrhage.

- Balloon dilatation of PUJ obstruction in infants and children is technically feasible, safe and viable alternative to open or laparoscopic pyeloplasty.
- Ante grade (percutaneous) balloon dilatation:
  - All dilatations are done under general anesthesia.
  - Under ultrasound guidance, a puncture is made in the renal pelvis, followed by insertion of a Teflon coated (0.014–0.035) guide wires into the renal pelvis and through the PUJ.
  - Balloon catheters (2, 3, or 4 mm in diameter) are passed over the guide wire and used to dilate the PUJ obstruction.
  - The flow through the PUJ is checked after dilatation and a double J-sent is inserted.
  - A cutting balloon is used to widen the area of stenosis and it is important during the process of dilatation to abolish the area of wasting which is confirmed radiologically under fluoroscopy.
- This is especially so in infants where surgery is technically difficult and in experienced hands its efficacy is comparable to open or laparoscopic pyeloplasty.
- Generally, balloon dilatation and stenting has a lower success rate than the open or laparoscopic pyeloplasty but this increases in experienced hands where the results Balloon dilatation however, has a low morbidity and no mortality, less cost, no scars and a short hospital stay.
- Balloon dilatation is an attractive alternative to open or laparoscopic pyeloplasty as first-line treatment for PUJ obstruction. This is specially so in infants where open and laparoscopic pyeloplasties are known to be technically difficultbecome comparable to those of open or laparoscopic pyeloplasty.

3.9 Post-operative Complications and Follow-Up

- Open surgical pyeloplasty is known to be associated with complications which include:
  - Urinary tract infection and pyelonephritis
  - Anastomotic leakage and urinary extravasation
  - Recurrent pelviureteric junction obstruction
  - Stenosis and stricture at the anastomosis site
- The treatment of postoperative urinary leakage:
  - Some surgeons advocate placing a drain adjacent to the anastomosis to provide drainage in case of a leak.
  - The drain can be removed 48–72 h postoperatively if there is no leak.
  - Others advocate insertion of a trans-anastomotic stent to keep the anastomosis open and drain the renal pelvis.
  - Some surgeons place a double J stent which is removed after few weeks.
  - Postoperative leak without a drain can be treated by placing a perianastomotic drain percutaneously under ultrasound guidance.
  - Other methods to control the leak include:
    - Placement of percutaneous nephrostomy
    - Placement of a ureteral stent
- Postoperative complications following endopyelotomy include:
  - Significant intraoperative bleeding if the endoscopic incision is made inadvertently into a major polar vessel.
  - Those with significant bleeding can be treated with emergency angiography and embolization of the bleeding vessel.
  - Postoperative urinary tract infection
  - Recurrence of PUJ obstruction.
- A follow-up ultrasound should be obtained approximately 4–12 weeks postoperatively to monitor the outcome.
- Over time, nearly all patients (up to 95 %) have radiographic improvement and resolution of their symptoms.
- Renal ultrasound is the main investigation for postoperative follow-up of patients with PUJ obstruction.

- The first renal ultrasound is performed 4–6 weeks postoperatively.
  - If the follow-up ultrasound shows improvement where there is decrease in the severity of hydronephrosis, the patient can then be followed by repeat ultrasound initially 1 year postoperatively and then every 2–3 years.
  - If the follow-up ultrasound does not show improvement in the degree of hydronephrosis, diuretic renography is performed to detect persistent obstruction, which may require an additional surgical procedure.

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4 Renal Tumors in Children

4.1 Introduction

- Renal tumors are rare in children, with some of them being highly treatable and usually curable.
- The type of tumor found through pathological examination is very predictive of the outcome of children with renal tumors.
- The determination of tumor type is very important so that the children can receive the appropriate therapy.
- Renal tumors in children comprise a spectrum ranging from the benign neonatal congenital mesoblastic nephroma to the highly malignant anaplastic Wilms' tumor and Rhabdoid tumor of the kidney.
- Many pediatric renal tumors were previously lumped together and categorized as Wilms tumor.
- However, in recent years several specific tumors have been recognized as distinct pathologic entities.
- These are separate from the classic Wilms tumor.
- Wilms tumor (nephroblastoma) is the commonest renal tumor and accounts for 87 % of pediatric renal tumors.
- Although Wilms tumor is the most common pediatric renal malignancy, it is often indistinguishable from other rare but more aggressive tumors like rhabdoid tumor of the kidney and renal clear cell sarcoma or the more benign tumors like mesoblastic nephroma.
- Currently, as a result of better understanding of these tumors and the multimodal approach to therapy, survival of these patients has improved to its current rate of more than 80 %.
- The diagnosis of renal tumors of childhood is based on:
  - Clinical presentation
  - Radiological evaluation
  - Histopathologic examination
- The clinical presentation and radiographic appearance of these tumors are not unique to each tumor, and the diagnosis can only be confirmed by histological evaluation.
- The histological diagnosis is also important to decide the most appropriate adjuvant treatment of these tumors as these tumors range from chemosensitive Wilms' tumors to nonchemosensitive renal cell carcinoma.
- As with most tumors, a staging system has been developed to categorize patients for the appropriate treatment.

- Patients with tumors confined to the kidney that can be removed completely have the best survival rate.
- Patients who have unfavorable histology are not very responsive to chemotherapy or radiation therapy and complete surgical excision is essential.
- There are several renal tumors in children and these include:

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A.H. Al-Salem, *An Illustrated Guide to Pediatric Urology*, DOI 10.1007/978-3-319-44182-5_4

Age at Presentation for Renal Malignancies

1. Wilms tumor
    - Unilateral Wilms tumor: 1–11 year (Mean 3.5 year)
    - Bilateral Wilms tumor: 2 months–2 year (Mean 15 months)
2. Nephroblastomatosis: 6–18 months
3. Renal cell carcinoma: 6 months–60 year (Commonly 10–20 year)
4. Mesoblastic nephroma: 0–1 year (Commonly 1–3 months)
5. Multilocular cystic renal tumor
    - Cystic nephroma: Adult female
    - Cystic partially differentiated nephroblastoma: 3 months–4 year (Commonly 1–2 year)
6. Clear cell sarcoma: 1–4 year (Mean 2 year)
7. Rhabdoid tumor: 6 months–9 year (Commonly 6–12 months)
8. Angiomyolipoma: 6–41 year (Mean 10 year)
9. Renal medullary carcinoma: 10–39 year (Mean 20 year)
10. Ossifying renal tumor of infancy: 6 days–14 months (Commonly 1–3 months)
11. Metanephric adenoma: 15 months–83 year
12. Lymphoma
    - Hodgkin lymphoma: >10 year (Commonly late teens
    - Non-Hodgkin lymphoma: Any age (Commonly child <10 year)

– Wilms' tumor
– Cystic partially differentiated nephroblastoma
– Mesoblastic nephroma
– Renal cell carcinoma
– Clear cell sarcoma
– Rhabdoid tumor of the kidney
– Ossifying renal tumor of infancy
– Angiomyolipoma
– Neuroepithelial tumors of the kidney
– Lymphoma
– Renal medullary carcinoma
– Desmoplastic small round cell tumor of the kidney
– Others (Fibroma, Leiomyoma, Leiomyosarcoma, Primary renal synovial sarcoma, Anaplastic sarcoma of the kidney)

4.2 Wilms' Tumor

4.2.1 Introduction

- Wilms' (/vɪlmz/) tumor, or nephroblastoma is one of the commonest tumors of the kidneys that typically occurs in children.
- It is named after Dr. Max Wilms, the German surgeon (1867–1918) who first described it.
- Wilms' tumor, or nephroblastoma is a malignant tumor of the kidneys that typically occurs in children (Fig. 4.1).
- It makes up 87 % of pediatric renal tumors.
- Wilms tumor is the fourth most common childhood cancer.
- It is also the most common abdominal malignancy in children.
- Wilms' tumor accounts for 6–7 % of all childhood cancers.
- In North America about 450–500 new cases of Wilms tumor are diagnosed each year.

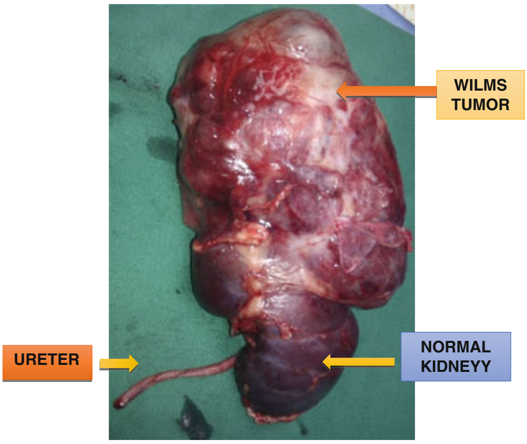


Fig. 4.1 A clinical photograph showing Wilms tumor arising from the upper part of the kidney

- Wilms tumor is relatively more common in blacks than in whites and is rare in East Asians.
- For unknown reasons, Wilms tumor is more common among children of African descent.
- Most cases of Wilms' tumor occur among children between 3 and 3.5 years old.
- Girls are slightly more likely to develop Wilms' tumor than are boys.
- The majority (75 %) of Wilms' tumor cases occur in otherwise normal children.
- In about 25 % of cases, Wilms' tumors are associated with other developmental abnormalities.
- Most nephroblastomas are unilateral affecting one kidney only.
- This however is not the case in patients with Denys-Drash syndrome who mostly have bilateral or multiple tumors.
- The majority of nephroblastomas are unilateral and bilateral Wilms tumor are seen in 5–10 % of cases.
- In 5–10 % of patients, both kidneys are affected:
  - At the same time (synchronous bilateral Wilms tumor).
  - Or one after the other (metachronous bilateral Wilms tumor).
- Wilms' tumor has a classic histologic picture which is called triphasic composed of epithelial, blastemal, and stromal elements.
- Approximately 80–90 % of Wilms' tumors have favorable histology.
- About 3–7 % of Wilms' tumors are characterized by anaplastic changes. If these changes are present diffusely throughout the tumor (diffuse anaplasia), they are predictive of a poor outcome.
- Wilms' tumors are usually encapsulated and vascularized and in cases of metastasis it is usually to the lungs.
- Two renal tumor types (Clear cell sarcoma of the kidney and Rhabdoid tumor of the kidney) were previously included in the category with unfavorable Wilms' tumors. Currently, these are considered separate malignant entities.
- The overall prognosis of Wilms' tumor following surgical excision is excellent and the survival of these patients has improved markedly over the years.
- At present, with early diagnosis and current multimodality therapy, approximately 80–90 % of children with Wilms tumor survive.
  - This is attributed to The National Wilms' Tumor Study Group (NWTSG) and the International Society of Pediatric Oncology (SIOP) who have identified several chemotherapeutic agents through their clinical trials.
- Wilms tumor arises from persistent metanephric blastemal.
- Pathologically, Wilms tumors are described as being triphasic made up of three elements:
  - Metanephric blastema
  - Stroma (mesenchyme)
  - Epithelium
- Add to this the presence of abortive tubules and glomeruli surrounded by a spindled cell stroma. The stroma may include striated muscle, cartilage, bone, fat tissue, and fibrous tissue.
- The mesenchymal component may include cells showing rhabdomyoid differentiation or malignancy (rhabdomyosarcomatous Wilms).
- Pathologically, Wilms tumors is divided into two prognostic groups:
  - Favorable: The tumor contains well developed components.
  - Anaplastic: The tumor contains diffuse anaplasia (poorly developed cells).
- It was shown that mutations of the WT1 gene on chromosome 11p13 are seen in approximately 20 % of Wilms tumors.
- At least half of the Wilms tumors with mutations in WT1 also carry mutations in CTNNB1, the gene encoding the proto-oncogene beta-catenin.
- It was shown also that a gene on the X chromosome, WTX, is inactivated in up to 30 % of Wilms tumor cases.
- A tumor biopsy is not typically performed due to the risk of creating fragments of cancer tissue and seeding the abdomen with malignant cells.
- Children with Beckwith-Wiedemann syndrome, WAGR syndrome and Denys-Drash

syndrome, have increased risk of Wilms tumor.

- There is a definite genetic predisposition to Wilms' Tumor in children with aniridia. This is due to deletions in the p13 band on chromosome 11.
- The treatment of unilateral Wilms' tumor is nephrectomy followed by chemotherapy, with or without postoperative radiotherapy. Chemotherapy regimens typically comprise vincristine and dactinomycin; doxorubicin and then cyclophosphamide and etoposide are added for increasingly high-risk disease.
- Wilms tumor may spread to the lungs, liver, or nearby lymph nodes.
- Wilms tumor is known to be associated with congenital anomalies:
  - Cryptorchidism (2.8 %)
  - Hemihypertrophy (2.5 %)
  - Hypospadias (1.8 %)
  - Sporadic aniridia
- Two loci on chromosome 11 have been implicated in the genesis of Wilms tumors.
  - Locus 11p13 is known as the WT1gene
  - Locus 11p15 is known as the WT2 gene.
  - An abnormal WT1 gene is present in patients with WAGR syndrome:
    - Wilms tumor
    - Aniridia
    - Genitourinary abnormalities
    - Mental retardation
  - An abnormal WT1 gene is present in patients with Denys-Drash syndrome:
    - Male pseudohermaphroditism
    - Progressive glomerulonephritis
  - An abnormal WT2 gene is present in patients with Beckwith-Wiedemann syndrome or hemihypertrophy.
  - The genetics of Wilms tumor appear to be multifactorial, and abnormalities at other sites, including chromosomes 1, 12, and 8, are also recognized.
  - Familial Wilms tumor is rare, occurring in approximately 1 % of cases and is not associated with mutations in chromosome 11.
- Screening for Wilms tumor in patients with associated syndromes should begin at 6 months of age with initial computed tomography (CT) followed by serial ultrasonography (US) every 3 months up to 7 years of age because the risk of developing Wilms tumor after the age of 7 years decreases significantly.
- Wilms tumor occasionally arises in the extrarenal retroperitoneum, presumably within mesonephric remnants (Extra Renal Wilms Tumor).
- The "teratoid Wilms tumor":
  - This is a Wilms tumor characterized by tissue differentiation within the tumor cells such as bone, cartilage, and muscle.
- The vast majority of Wilms tumors demonstrate favorable rather than unfavorable histopathologic findings and anaplasia correlates directly with a negative prognosis and resistance to chemotherapy. It is characterized by atypical mitoses or hyperchromatic cells with large nuclei.

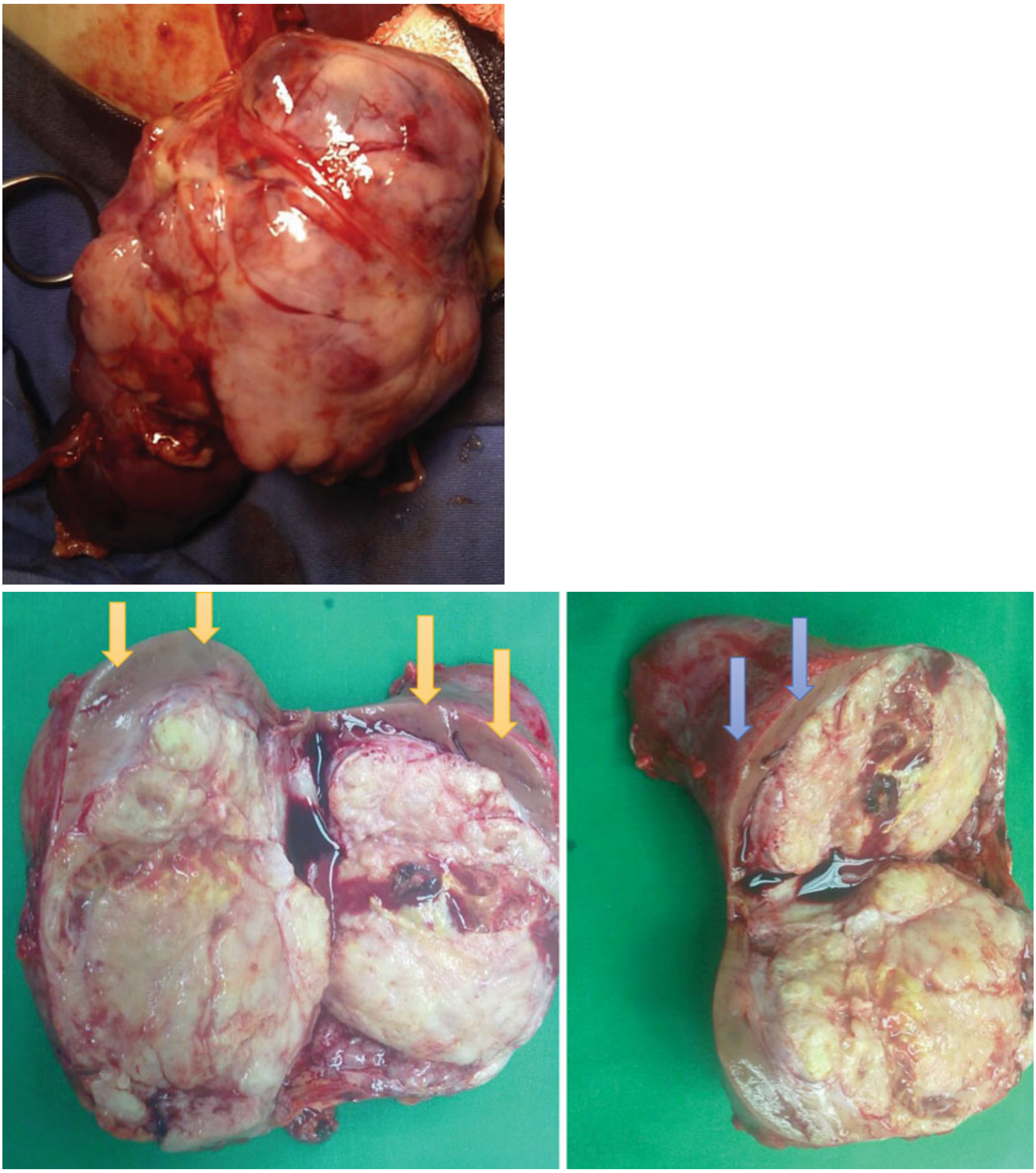
4.2.2 Etiology

- Wilms tumor is thought to be caused by alterations of genes responsible for normal genitourinary development.
- This is supported by the common congenital urological anomalies associated with Wilms tumor including:
  - Cryptorchidism
  - A double collecting system
  - Horseshoe kidney
  - Hypospadias
- WT1 gene and other genetic loci
  - WT1 encodes a transcription factor critical to normal renal and gonadal development.
  - WT1, the first Wilms tumor suppressor gene at chromosomal band 11p13, was identified in children with Wilms tumor who also had aniridia, genitourinary anomalies, and mental retardation (WAGR syndrome).
  - Karyotypic analysis revealed constitutional deletions within the short arm of 1 copy of chromosome 11.
  - The 11p13 locus was subsequently demonstrated to encompass numerous contiguous genes, including the aniridia gene *PAX6*

  and the Wilms tumor suppressor gene WT1.
  - A second gene that predisposes individuals to develop Wilms tumor has been identified at chromosomal band 11p15.
  - This locus was proposed on the basis of studies in patients with both Wilms tumor and Beckwith-Wiedemann syndrome (BWS).
  - Loci at 16q, 1p, 7p, and 17p have also been implicated in the biology of Wilms tumor, although these loci do not seem to predispose individuals to develop a Wilms tumor.
- Beckwith-Wiedemann syndrome (BWS):
  - This is an overgrowth syndrome characterized by visceromegaly, macroglossia, and hyperinsulinemic hypoglycemia.
  - Patients with BWS are predisposed to have several embryonal neoplasms, including Wilms tumor.
  - Several loci for Wilms tumor and BWS have been proposed. These loci include:
    - The insulinlike growth factor II gene (*IGFII*)
    - *H19*
    - p57kip2

4.2.3 Histopathology

- Wilms tumor arise as a solid intrarenal mass with a pseudocapsule.
- The tumor may also arise from one pole of the kidney.
- The tumor compresses the normal renal parenchyma and leads to distortion of the collecting system.
- Wilms tumor typically spreads by direct extension causing displacement but no encasement of tissues.
- There may be vascular invasion of the renal vein and inferior vena cava with occasional extension into the right atrium.
- Metastases are most commonly found in the lungs (85 % of cases), liver, and regional lymph nodes, and metastatic disease may also produce vascular invasion.
- Pathologically, Wilms' tumor (Figs. 4.2, 4.3, 4.4, 4.5, 4.6, and 4.7):
  - Is usually a large, solitary and encapsulated tumor.
  - It compresses the remaining normal kidney parenchyma.
  - On cut section, Wilms' tumor is soft, homogenous and Tan-gray in color and may contain areas of hemorrhage and necrosis.
- Histologically, Wilms' tumor is a malignant tumor composed of three elements (a triphasic nephroblastoma) (Figs. 4.8, 4.9, 4.10, 4.11, and 4.12):
  - Metanephric blastema
  - Mesenchymal stroma
  - Epithelium
- One of the characteristic histological features of Wilms' tumor is the presence of abortive tubules and glomeruli surrounded by a spindled cell stroma.
- The stroma may include striated muscles, cartilage, bone, fat tissue, and fibrous tissue.
- Rhabdomyosarcomatous Wilms:
  - The mesenchymal stroma may also include cells showing rhabdomyoid differentiation. The rhabdomyoid component may itself show features of malignancy. When this feature is present, it is called rhabdomyosarcomatous Wilms' tumor. This particular sub-type shows poor response to chemotherapy.
- Wilms' tumors may be separated into two prognostic groups based on pathologic characteristics:
  - Favorable: This contains well developed components.
  - Anaplastic (unfavorable): This contains anaplastic cells which could be focal or diffuse. This is associated with higher frequencies of relapse and death especially those with diffuse anaplasia.
- The anaplasia in Wilms' tumor is classified into two types depending on the extent:
  - Diffuse anaplasia
  - Localized anaplasia
- Approximately 90 % of all Wilms tumors have favorable histology.
- About 3–7 % of Wilms tumors are characterized by anaplastic changes.
- The presence of diffuse anaplasia throughout the tumor is a predictive of poor outcome.



Figs. 4.2, 4.3, and 4.4 Clinical photographs showing Wilms tumor. Note the compressed renal tissue at the periphery

- Clear cell sarcoma of the kidney and rhabdoid tumor of the kidney were included in the unfavorable histology in the past and currently these are considered as separate malignant tumors.
- The presence of nephrogenic rests, and dysplastic lesions of metanephric origin, are now believed to represent precursor lesions of Wilms tumor. These lesions are observed in approximately one third of kidneys affected by Wilms tumors.
- It was also shown that children younger than age 12 months diagnosed with perilobar nephrogenic rests have a markedly increased risk of developing a contralateral Wilms tumor.
- The National Wilms Tumor Study (NWTS) and Societe Internationale D'Oncologie Pediatrique

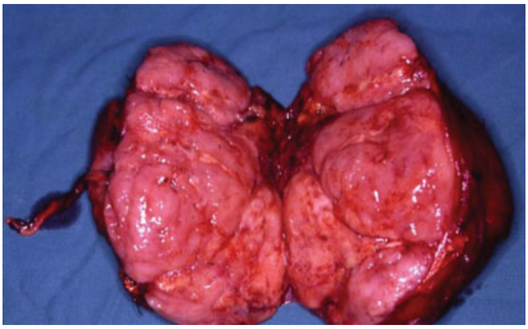


Fig. 4.5 A clinical photograph showing an excised Wilms tumor. Note the fleshy, homogenous and *Tan-gray* in color tumor

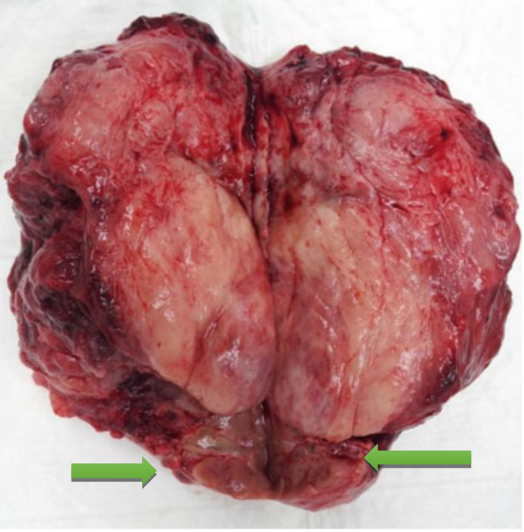


Fig. 4.6 A photograph of a resected Wilms' tumor. Note the gross appearance of Wilms' tumor with the normal part of the kidney being compressed by the tumor

(SIOP) have made large contributions to the modern multimodal treatment, which consists of surgical excision, radiotherapy, and chemotherapy (adjuvant and/or neoadjuvant). These oncologic treatments achieve a remarkable long-term overall survival rate of 90 %.

- Most cases of Wilms tumor do not have mutations in any of the genes.
- A gene on the X chromosome, WTX, is inactivated in up to 30 % of Wilms' tumor cases.
- The gene WT1:
  - This is also called Wilms tumor suppressor gene.

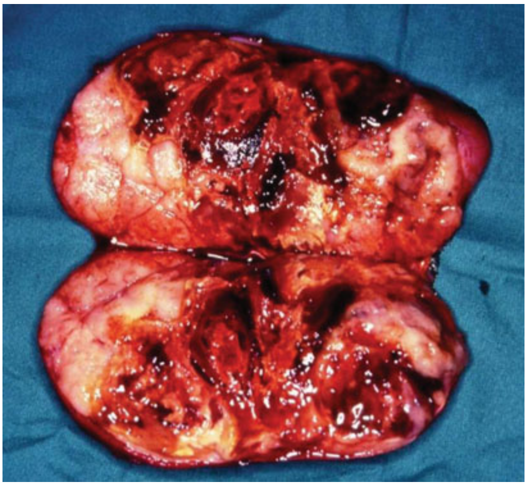


Fig. 4.7 A clinical photograph showing an excised Wilms tumor. Note the areas of hemorrhage within the tumor

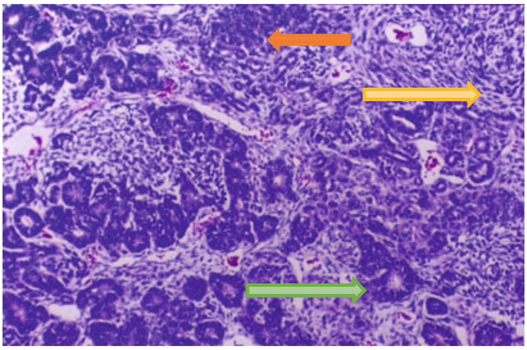
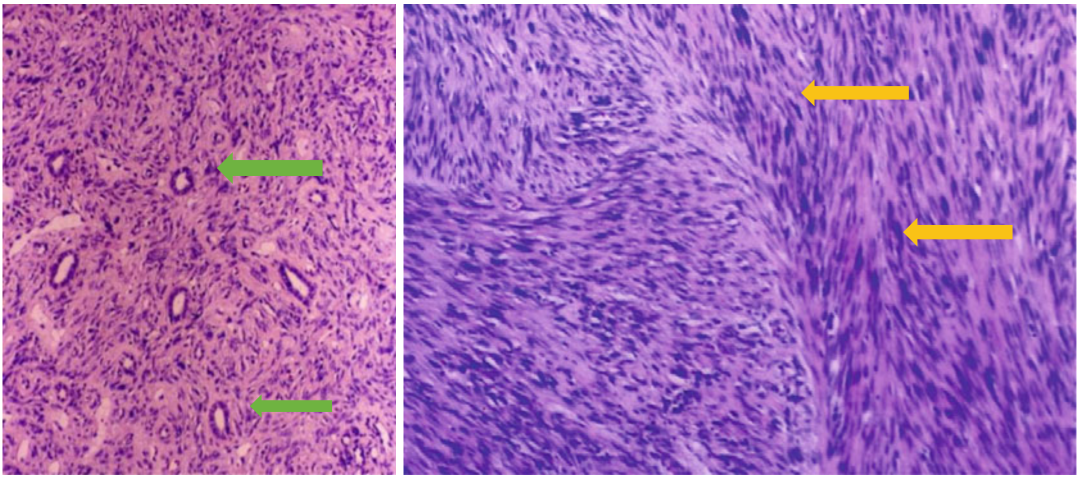
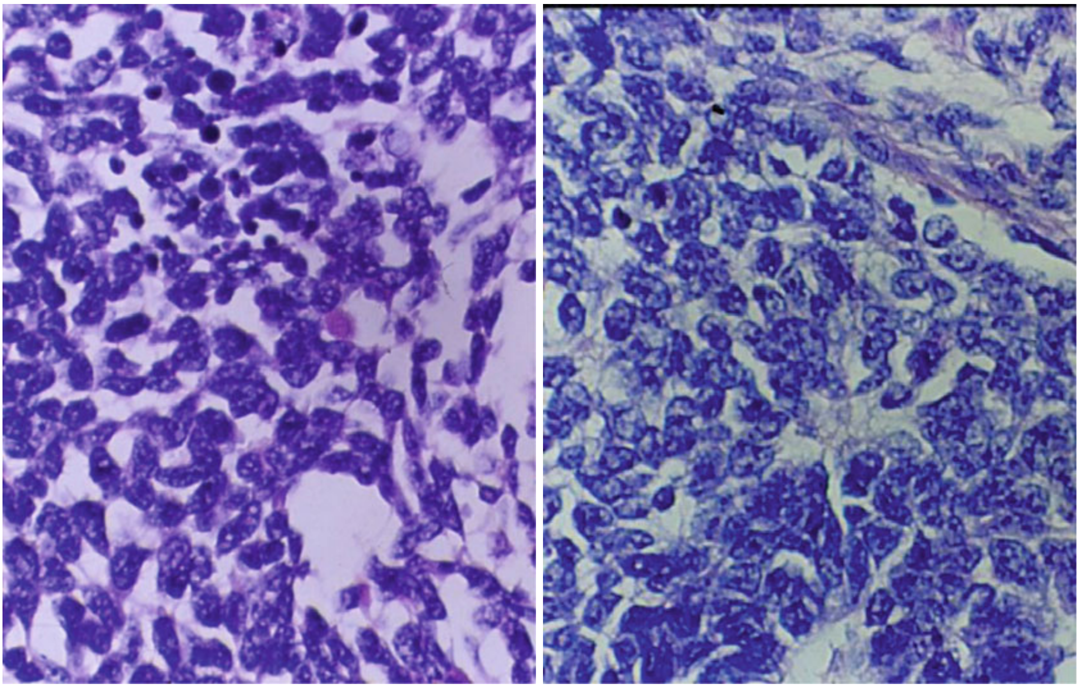


Fig. 4.8 A histological photograph of Wilms' tumor showing blastema (➡) tubules (➡) and spindle cells (➡)

  - It has been found to make a protein that is found mostly in the fetal kidney and in tissues that give rise to the genitourinary system.
  - Inactivation of this gene may be responsible for the occurrence of Wilms tumor.
  - Mutations of the WT1 gene on chromosome 11 p 13 are observed in approximately 20 % of Wilms' tumors.
  - At least half of the Wilms' tumors with mutations in WT1 also carry mutations in CTNNB1, the gene encoding the proto-oncogene beta-catenin.



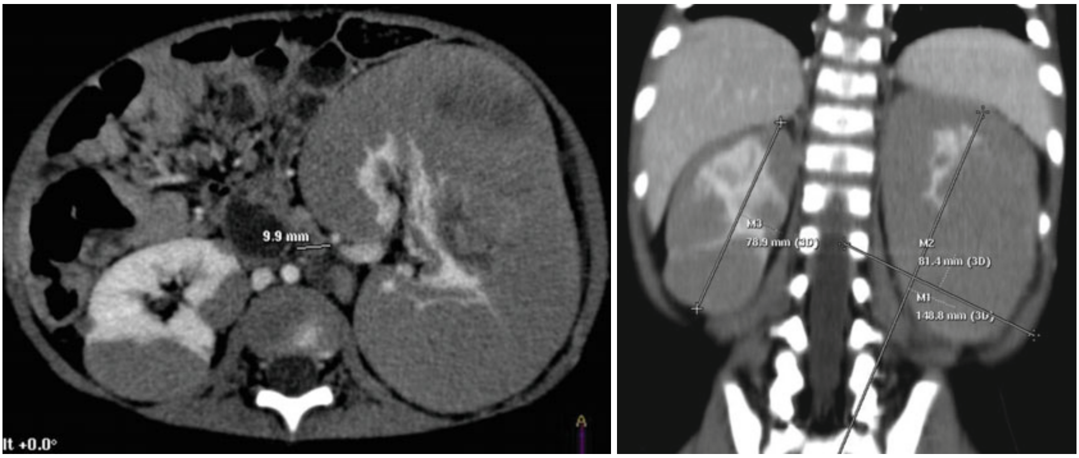
Figs. 4.9 and 4.10 Histological picture of Wilms' tumor showing tubules and spindle cells



Figs. 4.11 and 4.12 Histological pictures showing anaplastic Wilms' tumor. Note the large cells with large nuclei

4.2.4 Nephroblastomatosis

- The fetal kidney is formed by the development of nephrons from fetal metanephric blastema surrounding the ureteric bud.
- The fetal renal tissue matures into normal renal parenchyma during gestation, but, occasionally, fetal tissue persists into infancy as microscopic foci called nephrogenic rests (renal blastema).
- Renal blastema and nephroblastomatosis are interrelated conditions closely related to Wilms tumors (Figs. 4.13 and 4.14).
- The persistence of primitive renal blastema beyond 4 months of age is abnormal except in small microscopic rests.



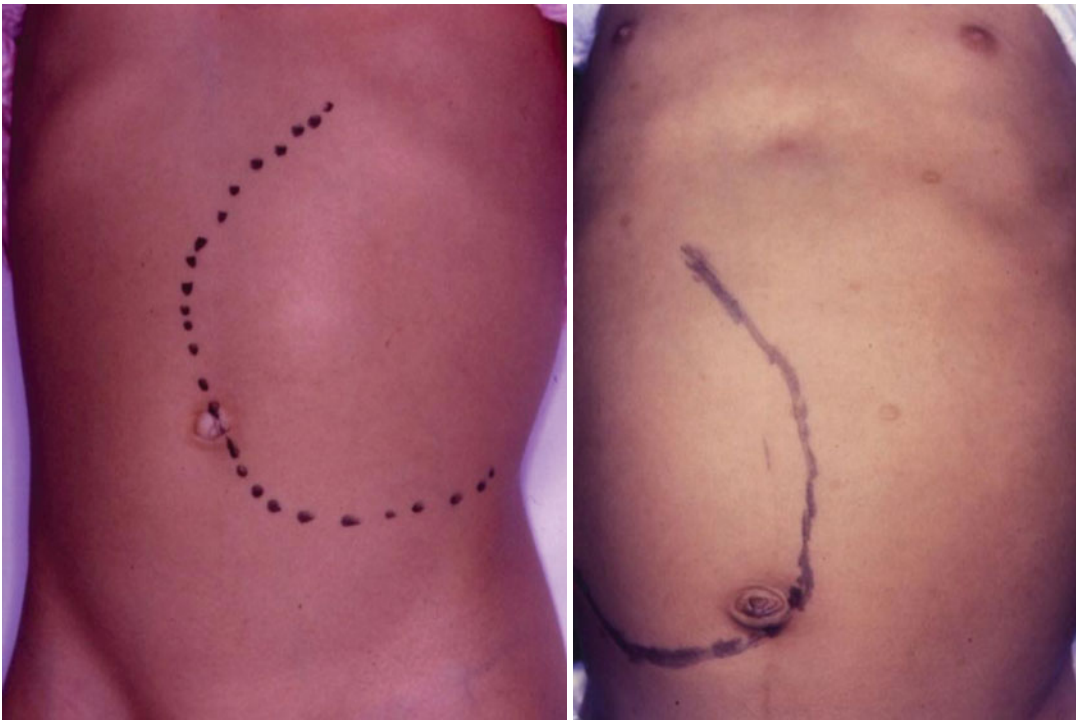
Figs. 4.13 and 4.14 Abdominal CT-scan showing bilateral nephroblastomatosis and Wilms' tumor

- Nephroblastomatosis is defined as the presence of multifocal nephrogenic rests.
- Nephrogenic rests are foci of metanephric blastema that persist beyond 36 weeks gestation and have the potential for malignant transformation into Wilms' tumor.
- Nephrogenic rest are found incidentally in 1 % of infants.
- It is currently believed that nephrogenic rests give rise to approximately 30–40 % of Wilms' tumors.
- Nephrogenic rests are found in up to 99 % of bilateral Wilms' tumors.
- Nephrogenic rests are classified histologically as:
  - Dormant, sclerosing, hyperplastic, or neoplastic.
  - Dormant and sclerosing rests are usually microscopic and are not considered to have malignant potential.
  - Hyperplastic and neoplastic rests are grossly visible as small tan nodules surrounded by normal parenchyma.
- There are two pathologic subtypes of nephrogenic rest based on location (perilobar and intralobar):
  - Perilobar rest (90 %)
  - Intralobar rest (10 %). This is more associated with Wilms' tumor.
  - Prilobar rests:
    - They are found in subcapsular location with well demarcated low power margins.
    - They are associated with Beck-with-Wiedemann syndrome and hemihypertrophy, Perlman syndrome (visceromegaly, gigantism, cryptorchidism, polyhydramnios, characteristic facies), and trisomy 18.
    - Malignant degeneration into Wilms tumor is most common in patients with Beckwith-Wiedemann syndrome and hemi-hypertrophy, occurring in 3 % of cases.
  - Intralobar rests:
    - These are considerably less common than the perilobar nephrogenic rest.
    - They present anywhere within the kidney and often have a more irregular and intermixed margins.
    - They have a higher association with Wilms tumor development.
    - These rests are found in 78 % of patients with Denys-Drash syndrome and nearly 100 % of patients with sporadic aniridia and are also seen in patients with WAGR syndrome.
  - Ultrasonographic detection of these rests is possible, but sonography lacks the sensitivity of CT and MRI.
  - On CT, macroscopic nephrogenic rests appear as low-attenuation peripheral nodules

  with poor enhancement relative to that of adjacent normal renal parenchyma.
  - On MRI, the nodules demonstrate low-signal-intensity foci on both T1-weighted and T2-weighted images.
  - On sonograms, the affected kidney may be enlarged and lobulated with multiple hypoechoic areas. Corticomedullary differentiation may be lost.
  - After such findings are discovered, three monthly ultrasound examinations should be performed to detect their progression to a Wilms' tumor.
  - Lymphoma can mimic the appearance of nephroblastomatosis but is unusual in infants and young children.
- Treatment for nephrogenic rests:
  - This is controversial.
  - Some investigators recommend chemotherapy, whereas others maintain that close serial radiologic evaluation of enlarging masses is sufficient.
  - Screening for Wilms tumor in patients with syndromes associated with nephrogenic rests should be performed.
  - Ultrasound is a good follow-up investigation, cheap, readily available and can be done easily without anesthesia, however CT-scan is the method of choice for follow-up.
  - On imaging, nephroblastomatosis appear as discrete, homogeneous, non-enhancing renal masses.
  - Any rapid growth, inhomogeneity, or heterogeneous enhancement should be taken seriously and worrisome for development of Wilms.

4.2.5 Clinical Features

- The usual presentation of Wims' tumor is with a painless abdominal mass discovered accidently by the parents or by a physician during a routine physical examination. It is not uncommon for the mother to discover the mass while giving bath to her child. This is the presentation in more than 80 % of children with Wilms tumor.
- The mass is discovered after coincidental trauma in up to 10 % of cases.
- Abdominal pain (25 %)
- Wilms' tumor can present with (Figs. 4.15, 4.16, 4.17, and 4.18):
  - Abdominal swelling or distension
  - Abdominal mass
  - Abdominal pain
  - Fever
  - Nausea and vomiting
  - Hematuria
  - Hypertension
  - Urinary tract infection
  - Wilms' tumor can grow rapidly as a result of bleeding into the tumor or from actual tumor growth.
  - Bleeding into the tumor will lead to anemia and if severe will result in heart failure.
- Hematuria:
  - May be seen in 10–15 % of cases.
  - This can be microscopic or gross hematuria.
  - This is seen often after a relatively minor trauma and injury of the enlarged kidney by the tumor.
  - Hematuria may be seen as a late presentation that is usually associated with tumor invasion of the calyces and considered a bad prognostic sign.
- Hypertension:
  - As many as one third of patients with Wilms tumor present with hypertension. Their blood pressure usually normalizes after nephrectomy, but they occasionally require prolonged therapeutic intervention
  - Increased blood pressure may be present in 20 % of Wilms' tumor cases.
  - Hypertension in Wilms's tumor results from pressure effect of the tumor on the renal vessels leading to increased secretion of rennin.
- Rarely, the tumor may produce erythropoietin leading to increased red blood cells production and polycythemia.
- Patients with Wilms tumor can present with hemorrhage into their tumor leading to hypotension, anemia, and fever.
- Rarely patients with Wilms tumor and lung metastases may present with respiratory symptoms.
- Wilms' tumor can occur as part of rare genetic syndromes, including:



Figs. 4.15 and 4.16 Clinical photographs showing children with left and right Wilms tumors

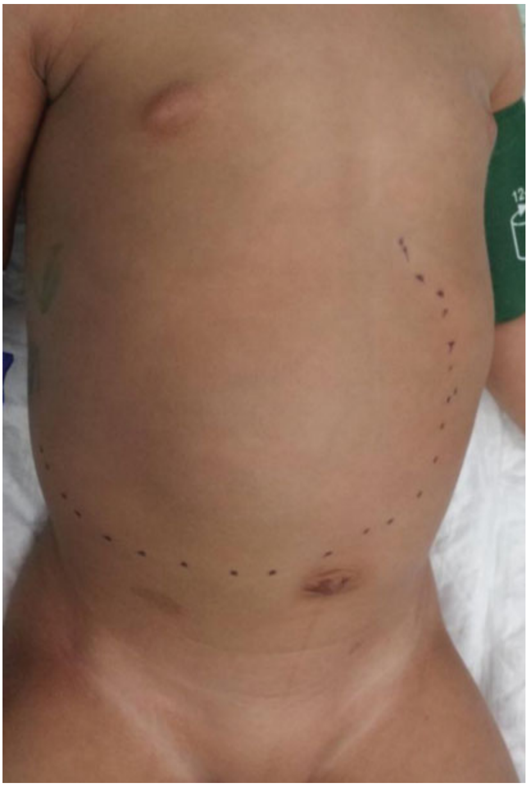


Fig. 4.17 A clinical photograph showing a very large Wilms tumor filling almost the whole abdomen

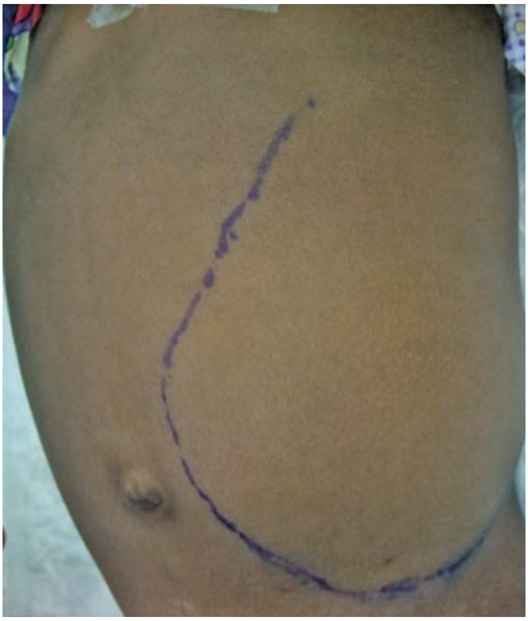


Fig. 4.18 A clinical photograph showing a very large Wilms tumor. This proved by abdominal CT-scan to be secondary to hemorrhage inside the tumor

  - WAGR syndrome. This syndrome includes:
    - Wilms tumor.
    - Aniridia.
    - Abnormalities of the genitals and urinary system.
    - Mental retardation.
  - Denys-Drash syndrome. This syndrome includes:
    - Wilms' tumor.
    - Kidney disease.
    - Male pseudohermaphroditism.
    - These patients mostly have bilateral or multiple tumors.
  - Beckwith-Wiedemann syndrome. This syndrome includes:
    - Omphalocele.
    - A large tongue (macroglossia).
    - Enlarged internal organs (visceromegaly).
    - Hypoglycemia.

4.2.6 Risk Factors for Wilms' Tumor

- Female gender
  - Girls are slightly more likely to develop Wilms' tumor than are boys.
- Black children have a slightly higher risk of developing Wilms' tumor than do children of other races.
  - People of African descent have the highest rates of Wilms' tumor.
- Children of Asian descent appear to have a lower risk of developing Wilms' tumor than do children of other races.
- A family history of Wilms' tumor increases the risk of developing Wilms' tumor.
- Wilms' tumor occurs more frequently in children with certain congenital abnormalities, including:
  - Aniridia (partial or total absence of the iris)
    - A genetic predisposition to Wilms' Tumor in individuals with aniridia has been established, due to deletions in the p13 band on chromosome 11.
  - Hemihypertrophy
  - Undescended testicles
  - Hypospadias
  - A double collecting system
  - Horseshoe kidney
- Wilms' tumor can occur as part of rare syndromes, including:
  - WAGR syndrome: This syndrome includes Wilms' tumor, aniridia, abnormalities of the genitals and urinary system, and mental retardation.
  - Denys-Drash syndrome: This syndrome includes Wilms' tumor, kidney disease and male pseudohermaphroditism.
  - Beckwith-Wiedemann syndrome (BWS):
    - BWS is an overgrowth syndrome characterized by visceromegaly, macroglossia, omphalocele and hyperinsulinemic hypoglycemia.
    - Patients with BWS are predisposed to have several embryonal neoplasms, including Wilms' tumor.
    - Few candidate loci for Wilms' tumor and BWS have been proposed. These loci include the insulinlike growth factor II gene (*IGFII*), *H19* (for an untranslated ribonucleic acid [RNA]), and that encoding for p57kip2.
- WT1 gene:
  - WT1, the first Wilms' tumor suppressor gene at chromosomal band 11p13, was identified as a direct result of the study of children with Wilms' tumor who also had aniridia, genitourinary anomalies, and mental retardation (WAGR syndrome).
  - WT1 encodes a transcription factor critical to normal renal and gonadal development.
  - The WT1 gene is the specific target of mutations and deletions in a subset of patients with sporadic Wilms' tumors, as well as in the germline of some children (e.g., those with Denys-Drash syndrome) with a genetic predisposition to develop this cancer.
- Additional genetic loci:
  - A second gene that predisposes individuals to develop the Wilms' tumor has been identified (but has not yet been cloned) telomeric of *WT1*, at 11p15. This locus was proposed on the basis of studies in patients with both Wilms' tumor and Beckwith-Wiedemann syndrome (BWS), another

congenital Wilms' tumor predisposition syndrome linked to chromosomal band 11p15.
  - Loci at 16q, 1p, 7p, and 17p have also been implicated in the biology of Wilms tumor, although these loci do not seem to predispose individuals to develop a Wilms' tumor. Instead, they seem to be associated with the phenotype or the outcome.
- Wilms tumor may be part of a genetic syndrome and certain birth defects can also increase a child's risk for developing Wilms tumor.
- The following genetic syndromes and birth defects have been linked to Wilms tumor:
  - WAGR syndrome (Wilms tumor, aniridia, abnormal genitourinary system, and mental retardation)
  - Beckwith-Wiedemann syndrome (visceromegaly, macroglossia, and hyperinsulinemic hypoglycemia)
  - Hemihypertrophy
  - Denys-Drash syndrome
  - Cryptorchidism
  - Hypospadias
- It is recommended that children with these genetic syndromes and birth defects should be screened for Wilms tumor every 3 months until age 8 years.

4.2.7 Staging of Wilms Tumor

- Staging of Wilms tumor is based on anatomical findings and tumor cells pathology.
- The Children's Oncology Group staging of Wilms tumors:
- Stage I (43 % of patients)
  - Tumor is limited to the kidney and is completely excised.
  - The surface of the renal capsule is intact.
  - The tumor is not ruptured or biopsied (open or needle) prior to removal.
  - No involvement of extrarenal or renal sinus lymph-vascular spaces
  - No residual tumor apparent beyond the margins of excision.
  - Metastasis of tumor to lymph nodes not identified.
- Stage II (23 % of patients)
  - Tumor extends beyond the kidney but is completely excised.
  - No residual tumor apparent at or beyond the margins of excision.
  - Any of the following conditions may also exist:
    - Tumor involvement of the blood vessels of the renal sinus and/or outside the renal parenchyma.
    - The tumor has been biopsied prior to removal or there is local spillage of tumor during surgery, confined to the flank.
    - Extensive tumor involvement of renal sinus soft tissue.
- Stage III (20 % of patients)
  - Inoperable primary tumor.
  - Lymph node metastasis.
  - Tumor is present at surgical margins.
  - Tumor spillage involving peritoneal surfaces either before or during surgery, or transected tumor thrombus.
- Stage IV (10 % of patients)
  - Stage IV Wilms tumor is defined as the presence of hematogenous metastases (lung, liver, bone, or brain), or lymph node metastases outside the abdomenopelvic region (Fig. 4.19).
- Stage V (5 % of patients)
  - Stage V Wilms tumor is defined as bilateral renal involvement at the time of initial diagnosis (Figs. 4.20 and 4.21).

– In term of treatment and prognosis, for patients with bilateral Wilms tumor, it is important to stage each side separately according to the above criteria on the basis of extent of disease and plan treatment according to the side with the more advanced stage.

- The National Wilms Tumor Study Group (NWTSG) and the International Society of Pediatric Oncology (SIOP) have contributed to the overall improved survival of children with Wilms tumors. They improved our understanding of the molecular mechanisms that contribute to the development of Wilms tumor and identified several chemotherapeutic agents through clinical trials.

- Children with bilateral Wilms tumor are treated with preoperative chemotherapy. This is important because each kidney is staged separately, and preoperative chemotherapy may lead to complete resolution of disease in one kidney or reduction in the size of both tumors. This will make it possible to subsequently do nephrectomy on one side only or bilateral partial nephrectomies.

4.2.8 Investigations

- It is important to investigate children with Wilms tumor.

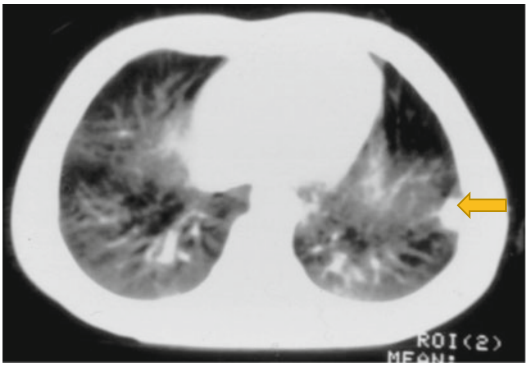
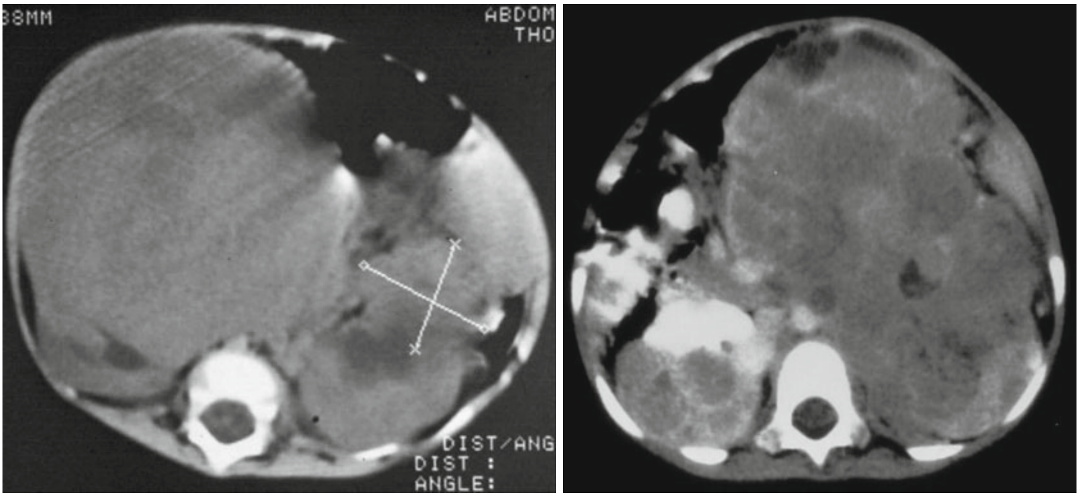


Fig. 4.19 CT-scan of the chest showing secondaries from Wilms tumor

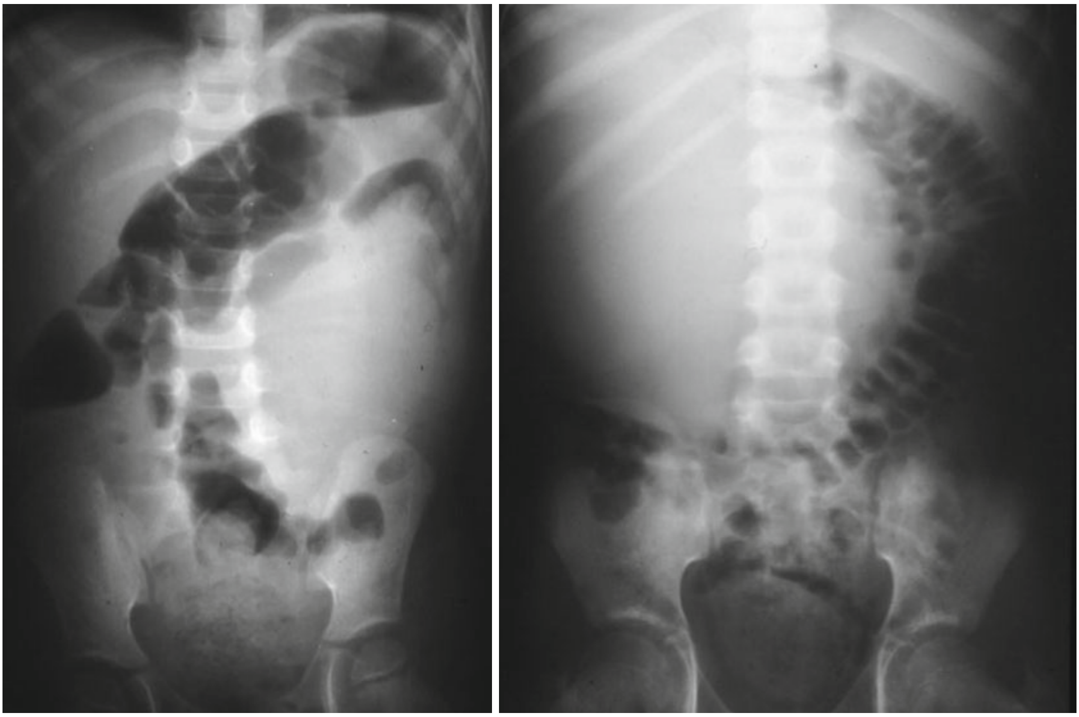
- The aim of the specific investigations is to evaluate the:
  - Site
  - Size
  - Extent of the tumor
  - Presence or absence of secondaries
  - Presence or absence of synchronous Wilms tumors
  - It is also important to make sure that there is a normally functioning contralateral kidney
- There are general and specific investigations.
- The general investigations include:
  - A complete blood count
  - Electrolytes
  - Liver function tests
  - BUN and creatinine
  - Urinalysis
  - Coagulation studies
  - Serum calcium
- It is of great importance to exclude extension of the tumor into the renal vein as well as the inferior vena cava.
- A plain abdominal radiograph (KUB) (Figs. 4.22 and 4.23):

– This often shows a soft tissue density with displacement of bowel loops inferiorly and to the contralateral side.

– Occasionally calcification (<10 %) is seen.

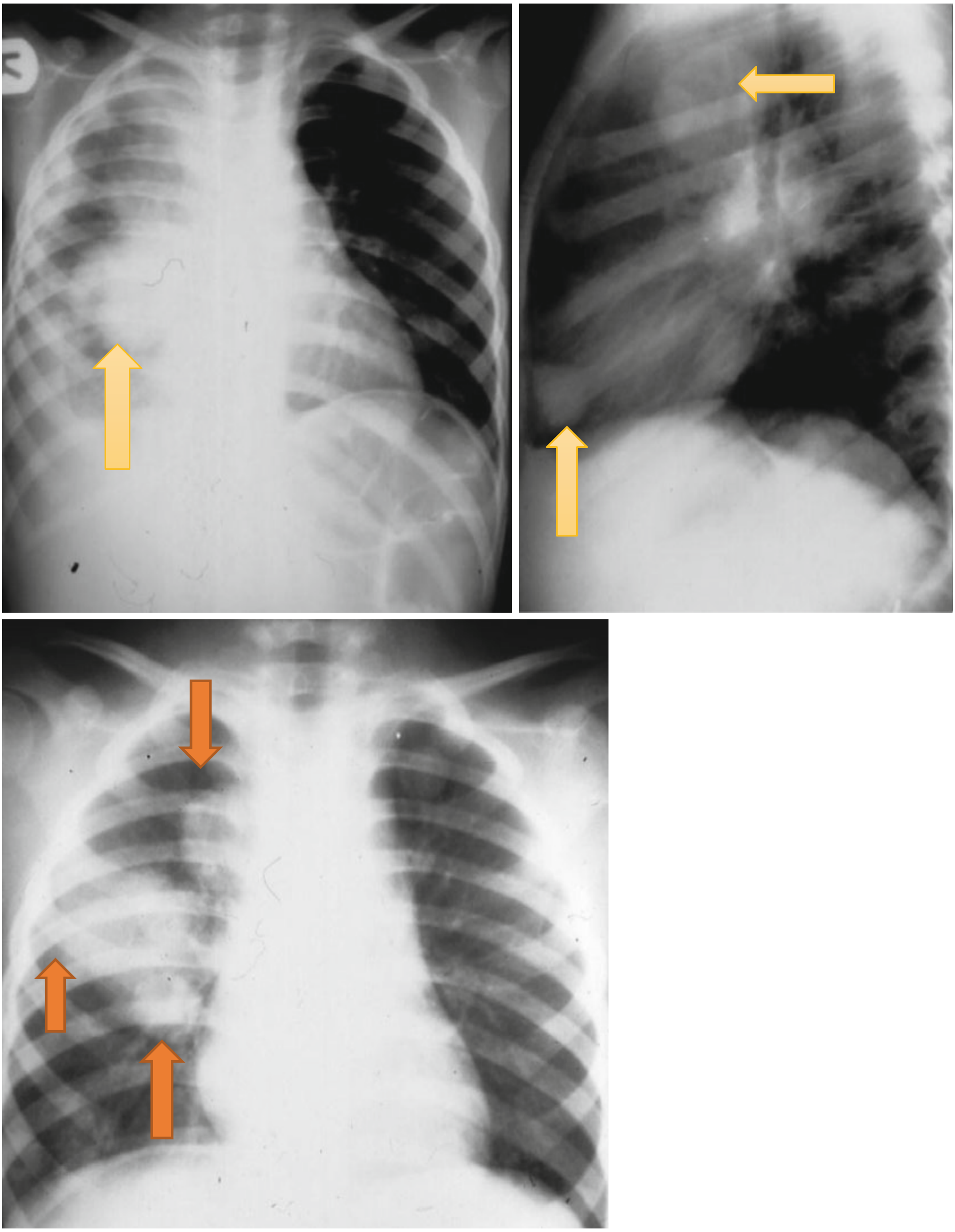


Figs. 4.20 and 4.21 Abdominal CT-scan in two patients with bilateral Wilms' tumor. The sizes of both tumors is different

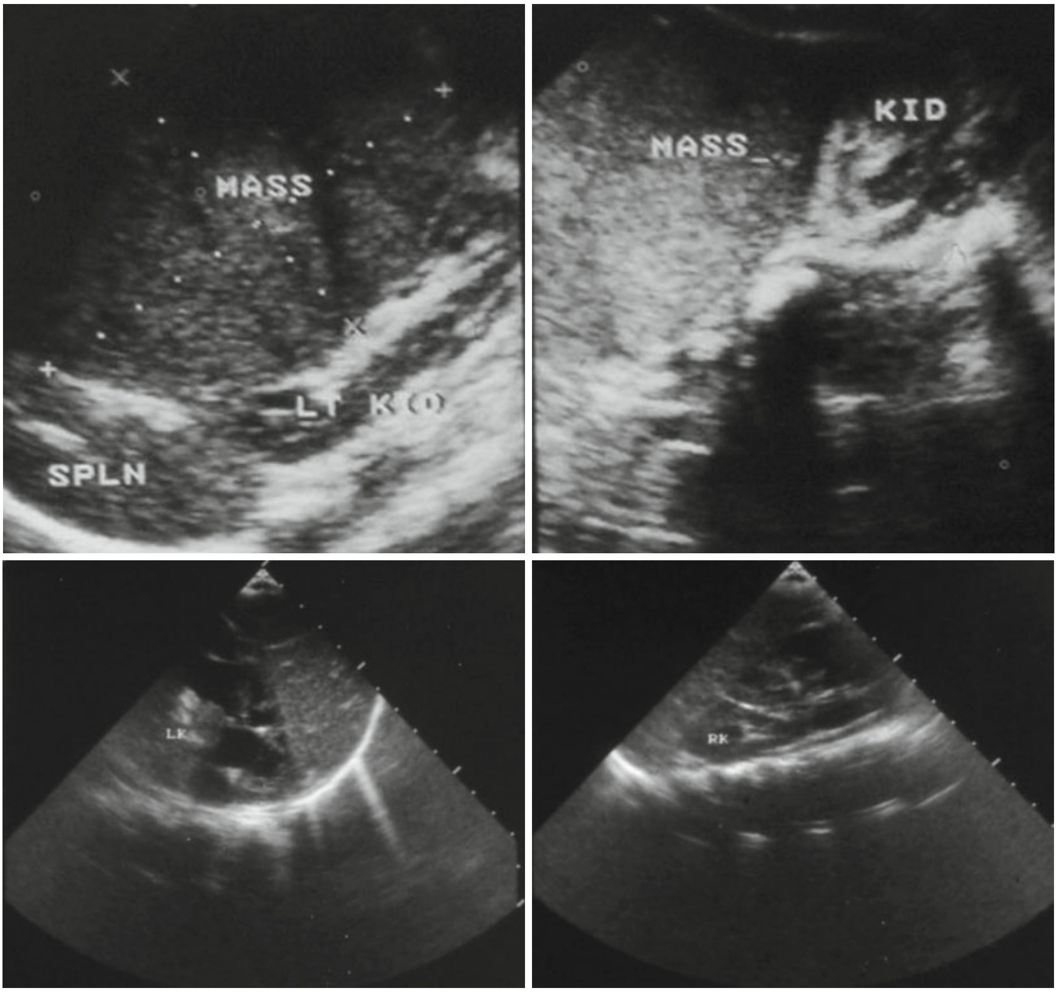


Figs. 4.22 and 4.23 Abdominal radiograph showing a soft tissue density in two patients with right and left Wilms tumor. Note the mass compressing and pushing the bowel downward and to the other side

  - The calcification usually is located on the edge of the tumor whereas calcification in neuroblastoma is speckled throughout.
- Chest radiograph (Figs. 4.24, 4.25, and 4.26):
  - This is to confirm or exclude the presence of secondaries in the lungs.
  - Distant metastasis in Wilms' tumor is commonly seen in the lungs.
  - CT-scan of the chest is more informative for the presence or absence of secondaries.
  - In children with Wilms' tumor. CT-scan of the chest and abdomen should be done simultaneously.
  - Abnormalities seen on chest CT-scan however, needs to biopsied to confirm the diagnosis.
- Abdominal ultrasound (Figs. 4.27, 4.28, 4.29, and 4.30):
  - This is valuable in determining the origin of the tumor, whether the mass is cystic or solid; and indicates if the tumor extends into the renal veins and inferior vena cava.
  - It is also useful in evaluating the contralateral kidney and whether a synchronous tumor is present or not.
  - Doppler ultrasound is a valuable investigation in detecting tumor extension in the renal vein and inferior vena cava and the extent of extension.
  - This shows a solid intrarenal mass.
  - The mass has heterogeneous echogenicity, which represents hemorrhage, fat, necrosis, or calcification.
- Abdominal and thoracic CT-scan (Figs. 4.31, 4.32, 4.33, 4.34, and 4.35):
  - This defines the tumor site; identifies the presence of enlarged lymph nodes; evaluates the contralateral kidney for possible presence of a second Wilms' tumor; assesses extension of the tumor into the renal veins, inferior vena cava and right atrium, and determines if the patient has intra-abdominal secondaries to the liver.
  - It is also valuable in detecting nodal metastases as well hemorrhage and areas of calcification within the tumor.
  - It is important to visualize the contralateral kidney and document that it is functioning using contrast.



Figs. 4.24, 4.25, and 4.26 Chest x-rays showing pulmonary secondaries from Wilms' tumor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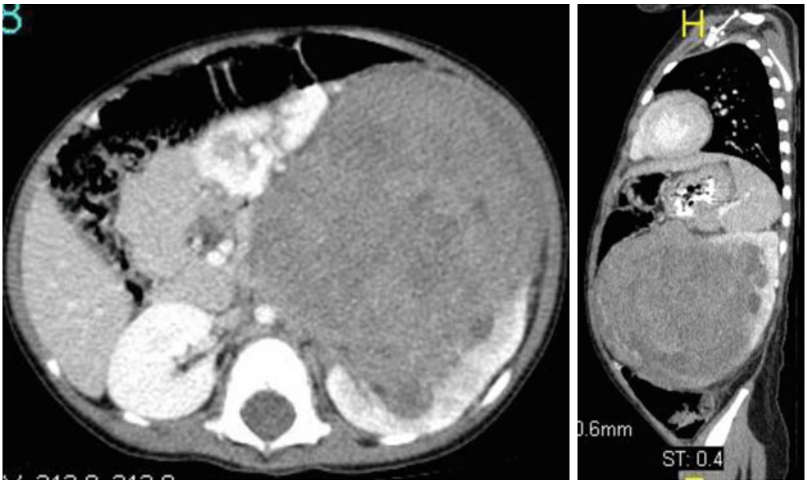
Figs. 4.27, 4.28, 4.29, and 4.30 Abdominal ultrasound showing left renal Wilms tumor in the upper one and bilateral Wilms tumor in the lower two pictures



Figs. 4.31 and 4.32 Abdominal CT-scan showing a very large left Wilms tumor

  - Thoracic CT-scan is important to detect pulmonary metastasis. Sometimes pulmonary metastasis are not seen on chest x-ray and appear only on CT-scan.
- Intravenous urography (Figs. 4.36, and 4.37):
  - In the past, this was one of the radiological investigation used to evaluate children with Wilms' tumor.
  - This is also useful to show that a normal functioning contralateral kidney is present.
  - Currently, this is replaced by CT-scan and MRI.
- MRI scanning (Figs. 4.38, 4.39, 4.40, 4.41, 4.42, and 4.43):
  - Abdominal magnetic resonance imaging (MRI) is reportedly the most sensitive imaging modality for determination of caval patency and may be important in determining whether the inferior vena cava is directly invaded by the tumor or not.

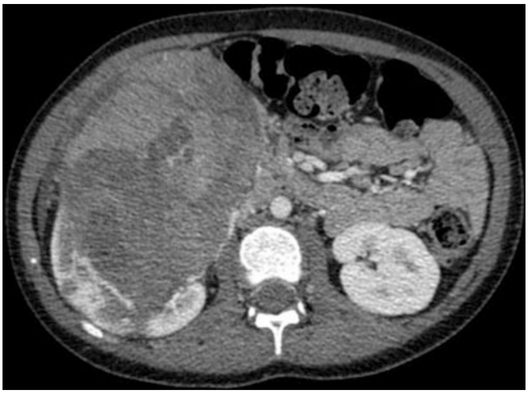
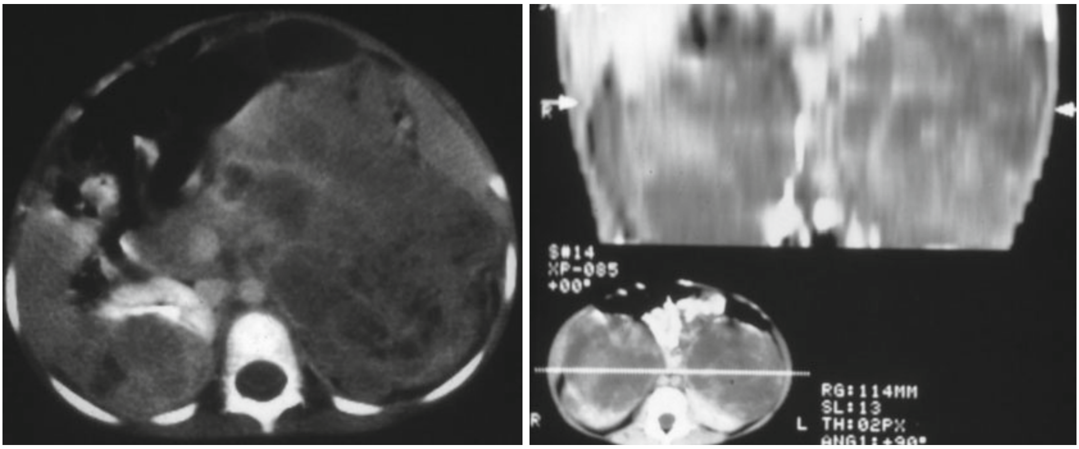
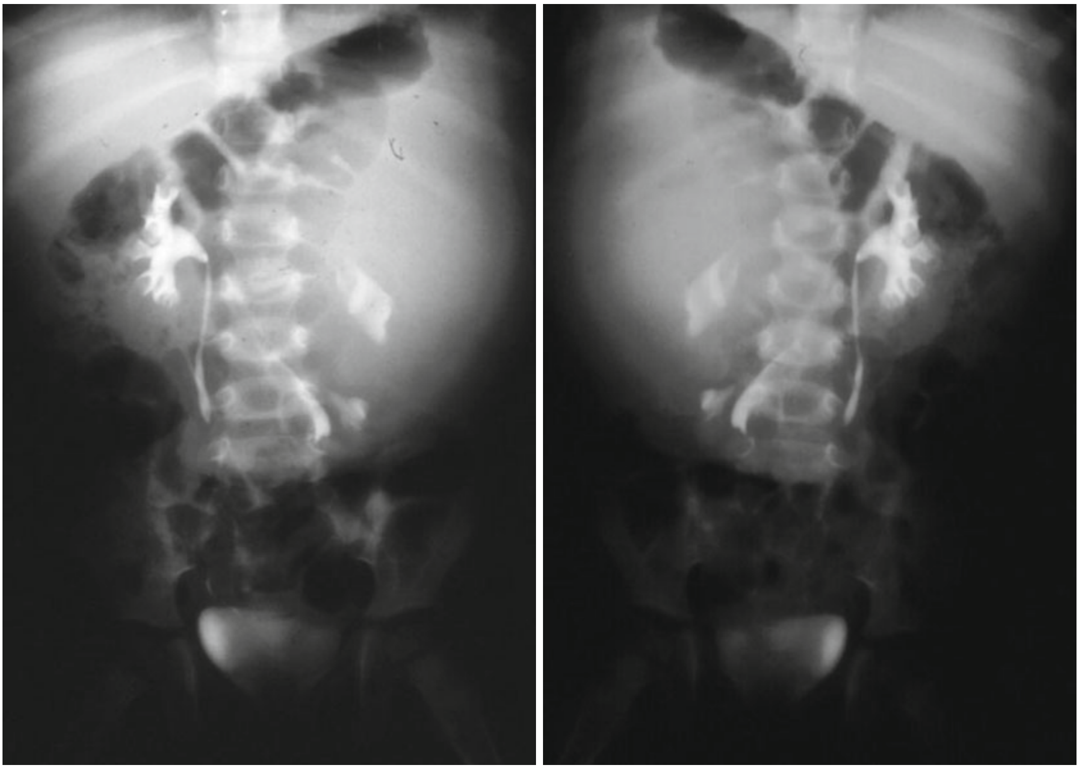


Fig. 4.33 Abdominal CT-scan showing a very large right Wilms tumor

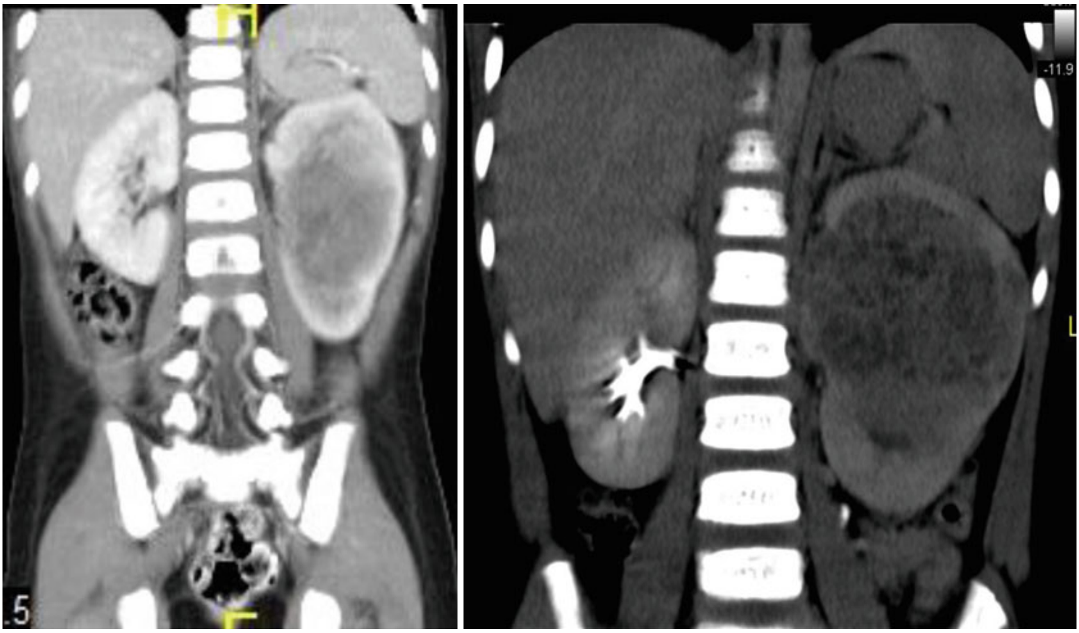
  - Wilms' tumor demonstrates low signal intensity on T1-weighted images and high signal intensity on T2-weighted images.
- Tumor extension into the renal vein and IVC is seen in 5–10 % of patients with Wilms tumor.
- A cystic variant of Wilms tumor may mimic benign multilocular cystic nephroma.
- Small abnormalities seen on chest x-ray are suggestive of secondaries but those seen on CT-scan may need to be confirmed by biopsy.
- With the current radiological investigations, physical inspection of the opposite kidney by opening Gerota's fascia as suggested previously to check for synchronous tumor is no longer necessary.
- Abdominal and chest CT-scan is useful in determining (Figs. 4.44, 4.45, 4.46, 4.47, 4.48, 4.49, 4.50, and 4.51):
  - The origin of the tumor
  - Involvement of the regional lymph nodes and local recurrence
  - Bilateral renal involvement
  - To visualize the contralateral kidney and document that it is functioning using contrast.
  - Invasion into the renal vein and inferior vena cava
  - Liver metastases
  - Lung metastases



Figs. 4.34 and 4.35 Abdominal CT-scans showing bilateral Wilms tumor

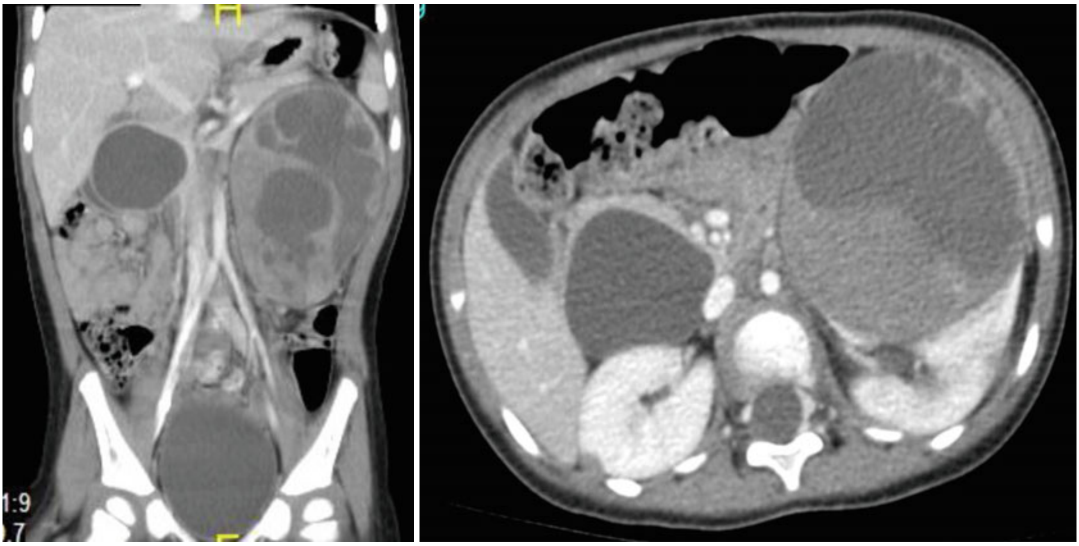


Figs. 4.36 and 4.37 Intravenous urography showing left and right Wilms tumors. Note the normal functioning contralateral kidney. Note also the distortion of the calcyeal system of the affected kidney

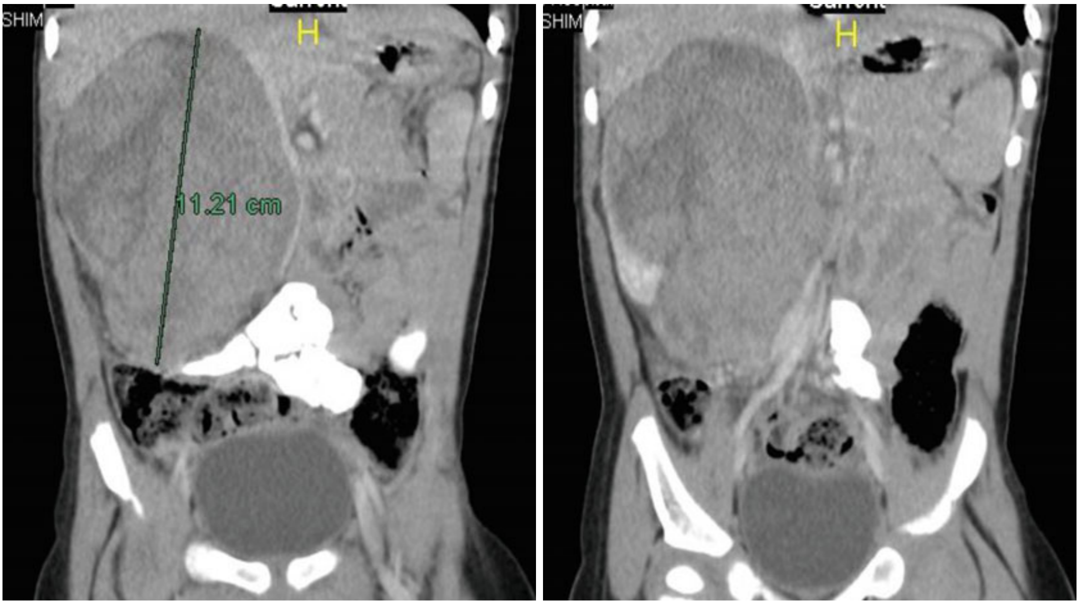


Figs. 4.38 and 4.39 Abdominal MRI showing left Wilms tumor. Note the normally functioning right kidney

- Diagnostic biopsy of lesions noted on the chest CT scan is recommended to confirm the diagnosis.
- Histopathologic confirmation of Wilms tumor is essential.
- Transcutaneous biopsy is not usually recommended as this may complicate treatment by causing preoperative tumor spill, requiring whole abdominal radiotherapy.
- – The National Wilms Tumor Study Group (NWTSG):
  - Patients with unilateral Wilms tumor undergo nephrectomy immediately.



Figs. 4.40 and 4.41 Abdominal MRI showing a large left side Wilms' tumor with areas of hemorrhage and or necrosis. Note also an associated congenital pancreatic cyst



Figs. 4.42 and 4.43 Abdominal MRI showing a large right side Wilms' tumor

  - During the procedure, the contralateral kidney is explored to ensure that the disease is indeed unilateral.
  - Lymph node biopsy samples are obtained for staging purposes. Lymph node dissection is not indicated.

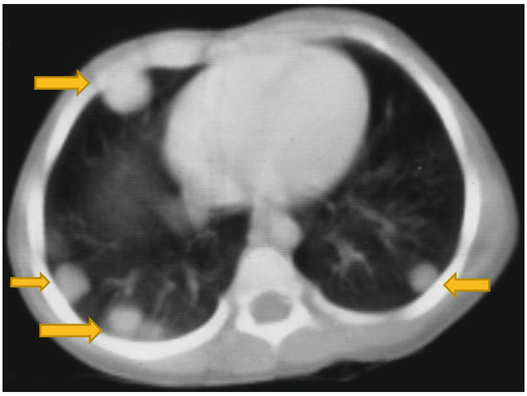


Fig. 4.44 CT-scan of the chest showing pulmonary metastasis from Wilms tumor

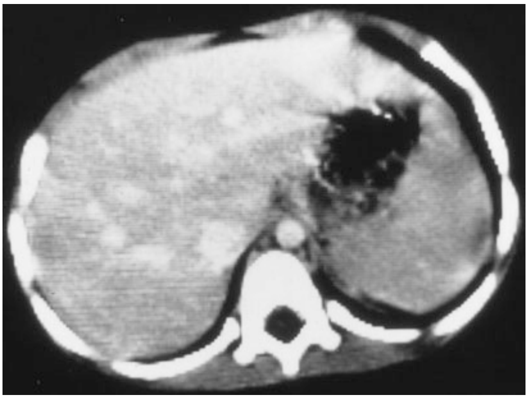
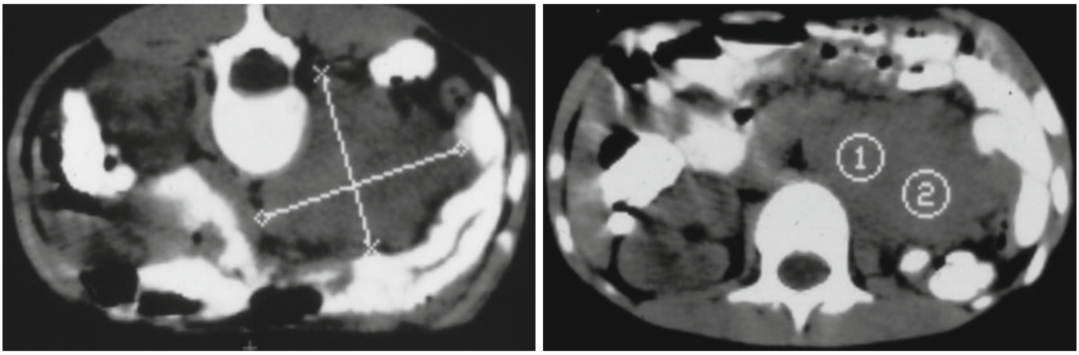


Fig. 4.45 CT-scan of the chest showing liver metastasis from Wilms tumor

- The International Society of Pediatric Oncology (SIOP)
  - The diagnosis of Wilms tumor is presumptive based on imaging findings alone.
  - Administration of chemotherapy
  - Nephrectomy

4.2.9 Prognosis and Complications of Wilms Tumor

- The prognosis is highly dependent on individual staging, histology and treatment.
- The overall 5-year survival is estimated to be approximately 80–90 %.
- Tumor-specific loss-of-heterozygosity (LOH) for chromosomes 1p and 16q identifies a subset of Wilms tumor patients who have a significantly increased risk of relapse and death. Children with loss of heterozygosity at 1p and 16q are treated with more aggressive chemotherapy.
- Approximately 80–90 % of children with a diagnosis of Wilms tumor survive with current multimodality therapy.
- Patients who have tumors with favorable histology have an overall survival rate of at least 80 % at 4 years after the initial diagnosis, even in patients with stage IV disease.
- The 4-year relapse-free and overall survival rates in patients with favorable-histology Wilms tumor are as follows



Figs. 4.46 and 4.47 CT-scans of the abdomen showing local recurrence following resection of Wilms tumor

Survival rates in patients with favorable-histology Wilms tumor

Stage	Relapse-free survival %	Overall survival, %
I	92	98
II	85	96
III	90	95
IV	80	90

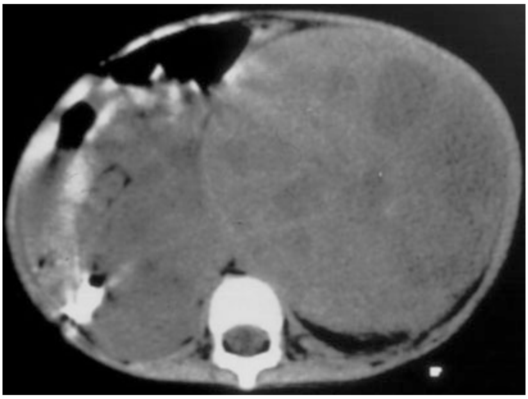


Fig. 4.48 Abdominal CT-scan showing bilateral Wilms' tumor

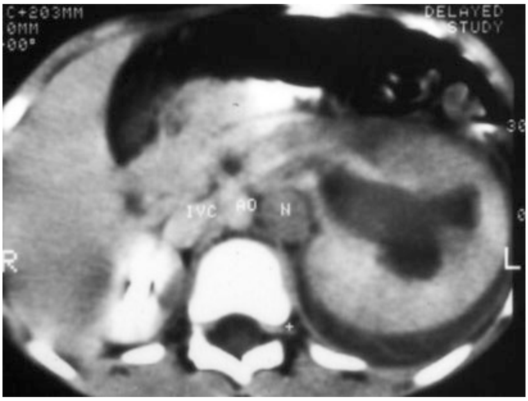


Fig. 4.49 Abdominal CT-scan showing left side Wilms' tumor. Note the patent IVC and the presence of an enlarged lymph node

- Patients with synchronous bilateral tumors have a 70–80 % survival rate, whereas those with metachronous tumors have a 45–50 % survival rate.
- Patients with anaplastic Wilms tumor have a worse prognosis compared with favorable histology Wilms tumor; the 4-year overall survival rates are 83 %, 83 %, 65 % and 33 % for stages I, II, III, and IV, respectively.

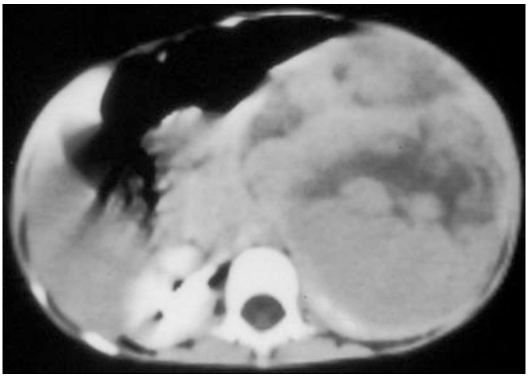


Fig. 4.50 Abdominal CT-scan showing a large left Wilms' tumor. Note the areas of hemorrhage or necrosis in the center

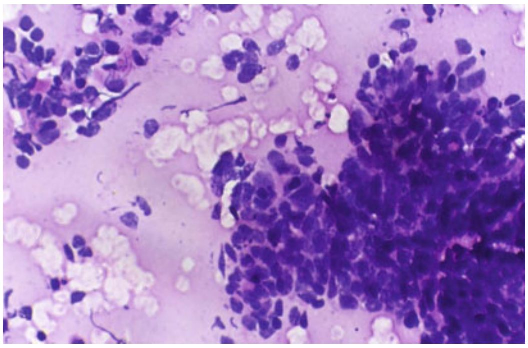


Fig. 4.51 Aspiration cytology showing cells of Wilms' tumor

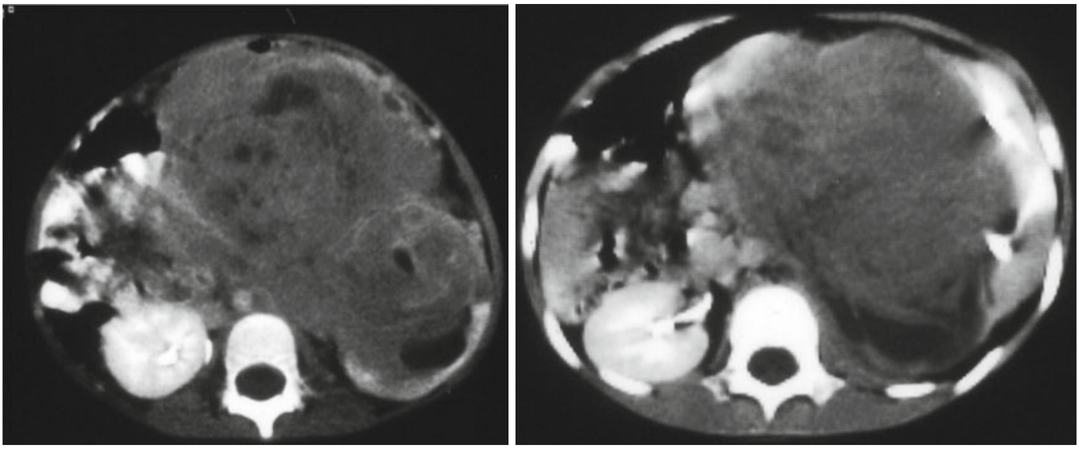
- Children with a loss of heterozygosity at 1p and 16q have a worse prognosis than do children without this heterozygosity loss.
- The prognosis for patients who have a relapse is not as good as it is for those with a newly diagnosed Wilms tumor, with 40–80 % of relapse patients expected to survive after salvage therapy.
- Chemotherapy and radiation therapy can induce second malignant neoplasms.
- Renal complications:
  - Children with unilateral Wilms tumor who undergoes nephrectomy have a minimal risk for impaired contralateral renal function.
  - There is usually a compensatory postnephrectomy hypertrophy of the remaining kidney.
  - The function of the remaining kidney may be affected in those who receive postoperative radiotherapy (Radiation-induced renal damage).

  - Renal function can be impaired in those with bilateral Wilms tumor.
  - The risk factors for renal damage include:
    - Stromal predominant histology
    - Intralobar rests
    - Age at diagnosis of younger than 24 months
    - Metachronous bilateral Wilms tumor
    - WT1 mutation etiology.
- Hepatic complications:
  - Hepatic damage in patients with Wilms tumor can be caused by radiation therapy and the use of cytotoxic drugs particularly dactinomycin and vincristine.
  - The dactinomycin hepatotoxicity is dose-related.
  - Radiotherapy is the main cause of hepatic toxicity but this rare nowadays.
  - Hepatic toxicity was reported in 2.8–14.3 % of children who did not receive radiotherapy.
  - Some patients with Wilms tumor have developed hepatic veno-occlusive disease.
    - Hepatic veno-occlusive disease is characterized by hepatomegaly or pain in the right upper quadrant, jaundice, ascites, and unexplained weight gain.
    - It is seen in children with Wilms tumor undergoing nephrectomy first and in those receiving combination chemotherapy before surgery.
- Other complications include:
  - Congestive heart failure is a well-known complication of the administration of anthracyclines (e.g. doxorubicin).
  - Radiation-induced pulmonary complications. This is more commonly seen in those who receive bilateral pulmonary irradiation.
  - Women who received whole-abdomen irradiation in childhood can develop ovarian failure.
  - Male patients are at risk for testicular failure after whole-abdomen radiation therapy or certain types of chemotherapy, most notably that involving alkylating agents.
  - Radiation therapy may affect the growth of any given bone but the spine is most notably affected. The effect is dose related and can lead to scoliosis.
  - There is an increased risk for second malignant neoplasm following chemotherapy and or radiotherapy.
    - Most secondary malignant neoplasms reported (e.g., bone tumors, breast and thyroid cancers) have occurred in irradiated areas.
    - Certain chemotherapeutic agents, including doxorubicin, dactinomycin, and vincristine, may contribute to an increased risk for secondary malignancies.
    - A recent interesting finding was that female survivors of Wilms tumor have a 9.1-fold increased risk of developing invasive breast cancer and had an estimated cumulative risk of invasive breast cancer at age 40 of 4.5 %. The risk was highest among children who had been treated with chest radiotherapy.

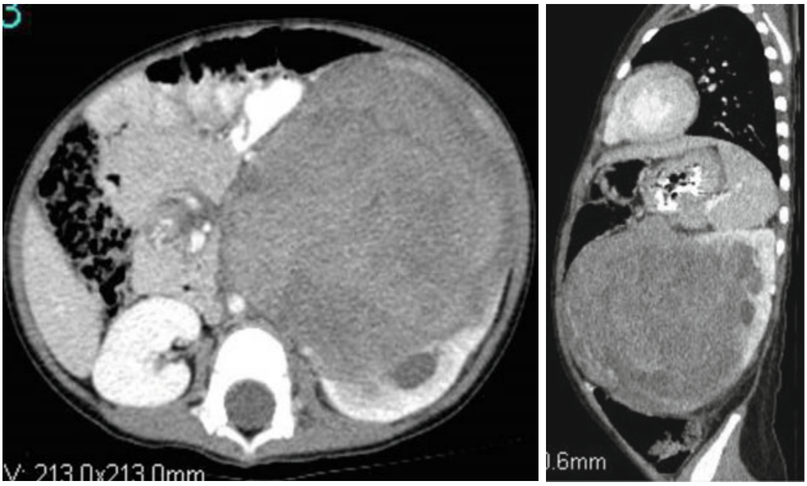
4.2.10 Surgical Considerations

- According to Children's Oncology Group (COG), the treatment of Wilms tumor is nephrectomy followed by chemotherapy, with or without postoperative radiotherapy.
- Certain children with stage I disease and favorable histology do well with nephrectomy alone.
- Radiotherapy:
  - Postoperative radiotherapy is started within 14 days of nephrectomy.
  - The current dose for radiation therapy for favorable histology Wilms tumor is approximately 1,080 cGy for the abdomen and 1,200 cGy for the lung.
  - Patients with stage IV favorable histology Wilms tumor and lung metastases whose pulmonary lesions do not disappear after 6 weeks of chemotherapy receive whole-lung radiation therapy.
- In North America:
  - Patients with suspected Wilms' tumor undergo nephrectomy immediately.
  - During this procedure, the contralateral kidney is explored to ensure that Wilms' tumor is unilateral.

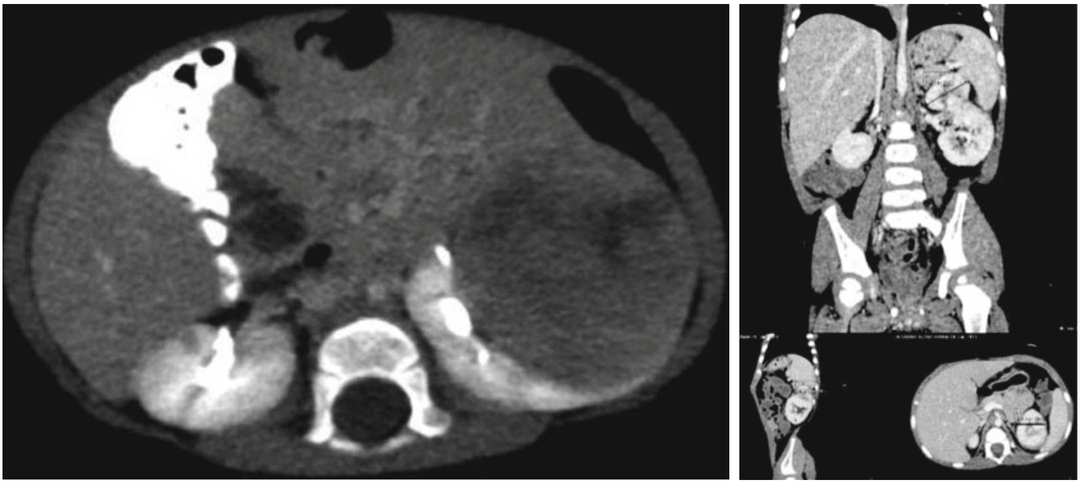
  - Currently, may surgeons will not explore the contralateral kidney and will depend on preoperative CT-scan or MRI evaluation.
  - Lymph node biopsy samples are obtained for staging purposes.
  - Immediate nephrectomy is not performed in patients with bilateral Wilms' tumor or those with very large unresectable Wilms tumor.
- In most European centers:
  - A presumptive diagnosis of Wilms' tumor is made based on imaging findings alone.
  - Administer chemotherapy before nephrectomy.
- Transcutaneous biopsy is not usually recommended and may in fact complicate treatment by causing preoperative tumor spill, requiring whole abdominal radiotherapy.
- Aspiration cytology is a valuable investigation to diagnose Wilms' tumor but it requires a good pathologist to read it (Fig. 4.51).
- The usual approach in most patients is nephrectomy followed by chemotherapy, with or without postoperative radiotherapy.
- Children found to have loss of heterozygosity at 1p and 16q receive more aggressive chemotherapy because they have a worse prognosis than do children without this heterozygosity loss.
- Children younger than age 12 months diagnosed with perilobar nephrogenic rests have a markedly increased risk of developing a contralateral Wilms' tumor.
- The National Wilms' Tumor Study Group (NWTSG) and the International Society of Pediatric Oncology (SIOP) have identified several chemotherapeutic agents through their clinical trials.
- At present, survival rates of children with Wilms' tumor are approximately 80–90 %.
- Chemotherapy without initial surgical resection can be used in the following situations:
  - Inoperable tumors (Figs. 4.52, 4.53, 4.54, 4.55, 4.56, and 4.57):
- Large tumors that involve vital structures make resection difficult; the complication rate is high, and the incidence of tumor rupture and spill is also high.
  - Intracaval tumor extension:
    - This occurs in 5 % of cases of Wilms' tumor.
    - This is associated with a 40 % rate of surgical complications.
    - Chemotherapy after staging and biopsy is beneficial in reducing the tumor and thrombus size.
  - Bilateral Wilms' tumor (Figs. 4.58, 4.59, 4.60, 4.61, 4.62, and 4.63).
- SIOP advocates chemotherapy without previous laparotomy and biopsy. The NWTSG suggests that this approach results in a 1–5 % risk of treating a benign disease.
  - Chemotherapy without proper surgical staging (e.g., staging by means of imaging



Figs. 4.52 and 4.53 CT-can showing large Wilms Tumors that appear inoperable



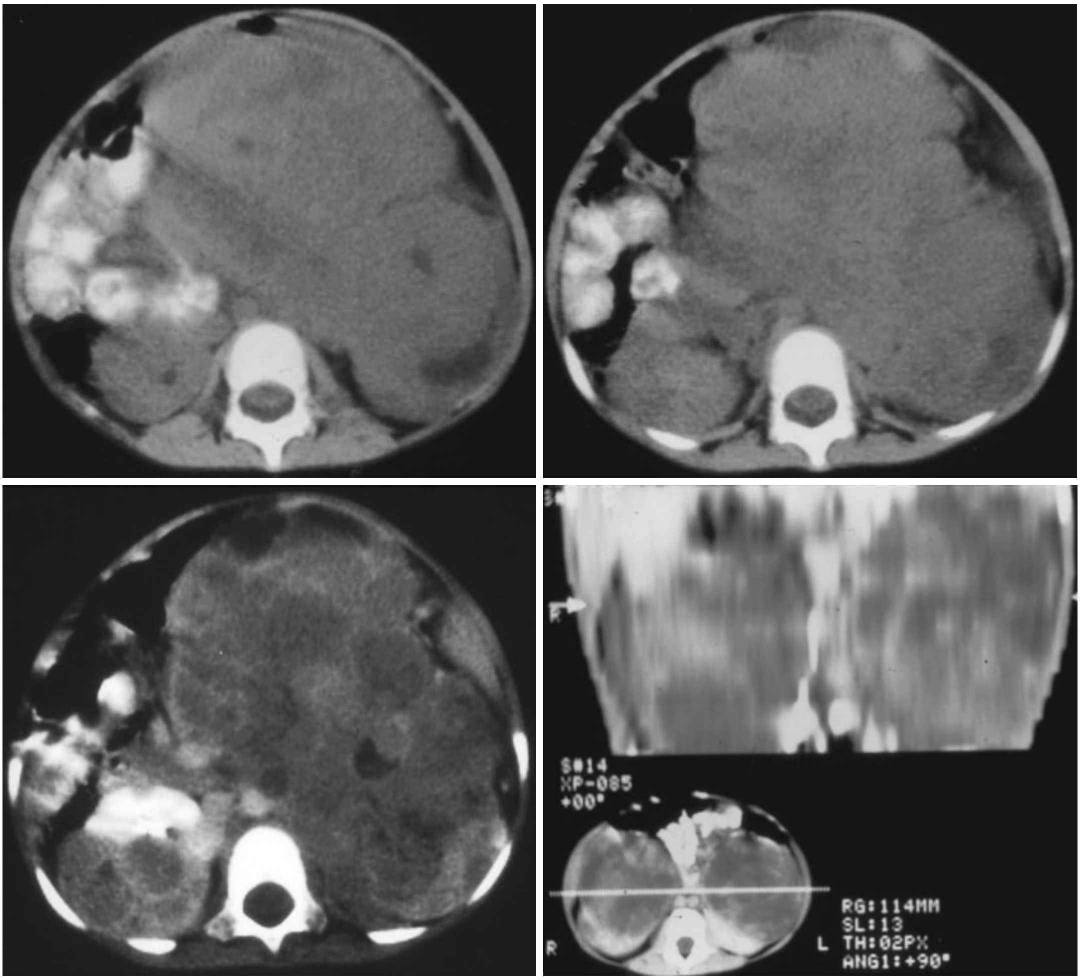
Figs. 4.54 and 4.55 CT-scan showing large left sided Wilms tumor



Figs. 4.56 and 4.57 Radiological evaluation of a large left Wilms tumor that was treated with preoperative chemotherapy showing an excellent response

studies only) may alter the actual initial stage of the disease by the time of surgery and may subsequently alter decisions regarding the adjuvant chemotherapy and radiation therapy, which is based on the surgical staging.

- Postoperative chemotherapy and radiotherapy protocols are based on the surgical staging and follow the guidelines of the NWTSG.
- Stage I:
  - Nephrectomy ±18 weeks of chemotherapy depending on age of the patient and weight of tumor.
  - A child less than 2 years old and a tumor less than 550 g only requires Nephrectomy and observation.
- Stage II:
  - Nephrectomy + abdominal radiation + 24 weeks of chemotherapy.
- Stage III:
  - Abdominal radiation + 24 weeks of chemotherapy + nephrectomy after tumor shrinkage.
- Stage IV:
  - Nephrectomy + abdominal radiation + 24 weeks of chemotherapy + radiation of metastatic site as appropriate.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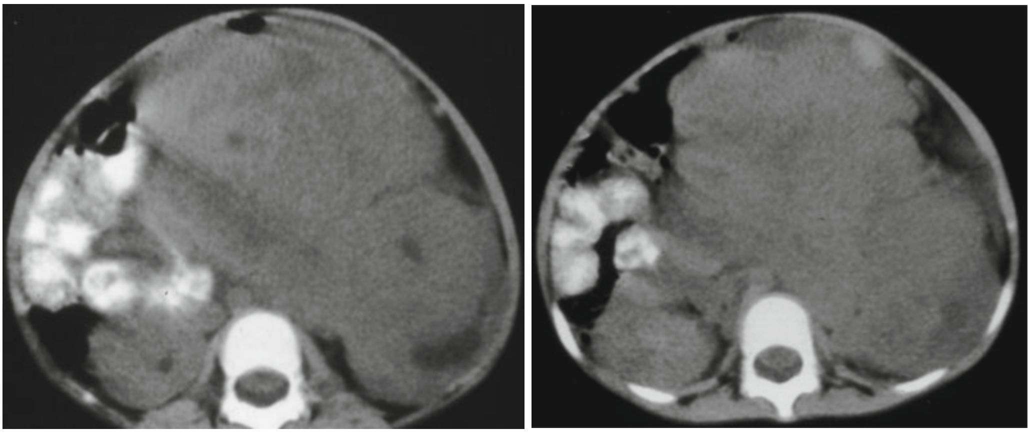
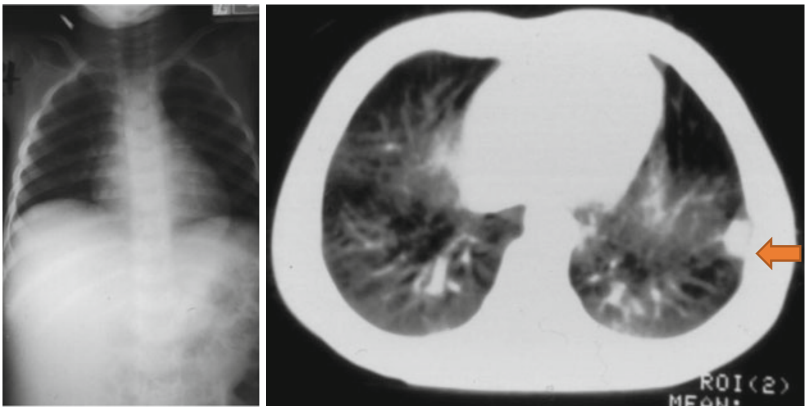
Figs. 4.58, 4.59, 4.60, and 4.61 Abdominal CT-scans showing bilateral Wilms tumors



Figs. 4.62 and 4.63 Abdominal CT-scans showing bilateral Wilms tumor before and after chemotherapy. Note the excellent response to chemotherapy with complete disappearance of Wilms tumor on one side and marked reduction of the tumor on the other side

- Stage V:
  - Individualized therapy based on tumor burden.
- The management of bilateral Wilms' tumor must be individualized according to the extent of tumor present in both kidneys with a goal to preserving adequate kidney tissue to avoid kidney failure.
  - The initial procedure should be biopsies of both kidneys to establish the diagnosis and histological types in both kidneys.
  - Approximately 4 % of cases have different types between the two kidneys.
  - The patient is treated with chemotherapy and restudied by abdominal CT or MRI to evaluate tumor response and determine whether a surgical procedure would be beneficial.
  - If considerable tumor persists in both kidneys, additional chemotherapy is administered, and surgery is delayed.
  - Radiation therapy is withheld if possible in these cases to reduce the risk of radiation injury to the remaining kidney tissue.
  - In some patients, the tumor persists in both kidneys, and resection of the tumor with preservation of functioning kidney tissue is not possible. The only remaining option for these rare patients ultimately is removal of both kidneys.
- Stage I–IV Anaplasia:
  - Children with stage I anaplastic tumors can be managed with the same regimen given to stage I favorable histology patients.
  - Children with stage II through stage IV diffuse anaplasia, however, represent a higher-risk group.
  - These tumors are more resistant to the chemotherapy traditionally used in children with Wilms' tumor (favorable histology), and require more aggressive regimens.
- About 5–10 % of patients with Wilms tumor present with acquired von Willebrand disease at the time of diagnosis.
- The reason for this acquired von Willebrand disease is not known ad several hypothesis have been postulated including:
  - Absorption of the von Willebrand factor (vWF) by tumor cells.
  - Hyperviscosity caused by elevated serum levels of hyaluronic acid.
  - An immunoglobulin G (IgG)–type antibody that prevents aggregation of normal platelet cells.
- The presence of acquired von Willebrand disease in these patients will lead to excessive bleeding during surgery and should be treated preoperatively.
- Desmopressin (DDAVP), a drug that promotes the release of vWF from storage sites, is recommended.
- If DDAVP is ineffective, cryoprecipitator (a specific vWF concentrate) should be administered.
- Management of lung metastasis (Figs. 4.64, 4.65, and 4.66):



Figs. 4.64 and 4.65 Abdominal and chest x-ray in a patient with right Wilms tumor and normal looking chest x-ray and chest CT-scan showing a single secondary in the chest

- A normal chest x-ray during initial evaluation does not exclude the presence of pulmonary metastasis and a chest CT-scan should be done as part of their evaluation.
- Children with normal looking chest radiography and positive findings on chest CT-scan require tissue diagnosis of the lung nodules.
- It is important to have tissue diagnosis of the lung nodules because several conditions (e.g. histoplasmosis, atelectasis, pseudotumor, intrapulmonary lymph node, pneumonia) can mimic pulmonary metastases.
- These secondaries can be single or multiple.
- A biopsy can be performed percutaneously or thoracoscopically.
- Single secondaries can be excised totally while multiple lesions are biopsied.
- Patients with favorable histology Wilms' tumor with lung metastasis and no other sites of distant spread or presence of 1p and 16q deletion are treated with 6 weeks of actinomycin-D, doxorubicin, and vincristine.

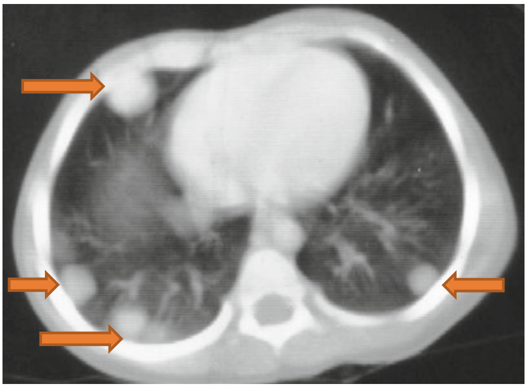


Fig. 4.66 Chest CT-scan showing multiple bilateral pulmonary secondaries in a child with Wilms tumor

4.2.10.1 Surgical Management (Figs. 4.67 and 4.68)

- The first step in the treatment of Wilms' tumor is surgical staging followed by radical nephrectomy, if possible.
- Begin the abdominal exploration through a transverse incision.
- The kidney is explored by mobilizing the ipsilateral colon and opening the Gerota fascia.
- Exploration of the contralateral kidney is currently not recommended because of the improvement in imaging techniques (computed tomography [CT] scanning, magnetic resonance imaging [MRI]).
- If the tumor is unresectable, biopsies are performed and the nephrectomy is deferred until after chemotherapy, which, in most cases, will shrink the tumor.
- Radical nephrectomy is the treatment of choice.
- If bilateral disease is diagnosed, nephrectomy is not performed, but biopsy specimens are obtained.
- New protocols in the management of bilateral Wilms' tumor are being explored. If the disease is unilateral, radical nephrectomy and regional lymph node dissection or sampling are performed.

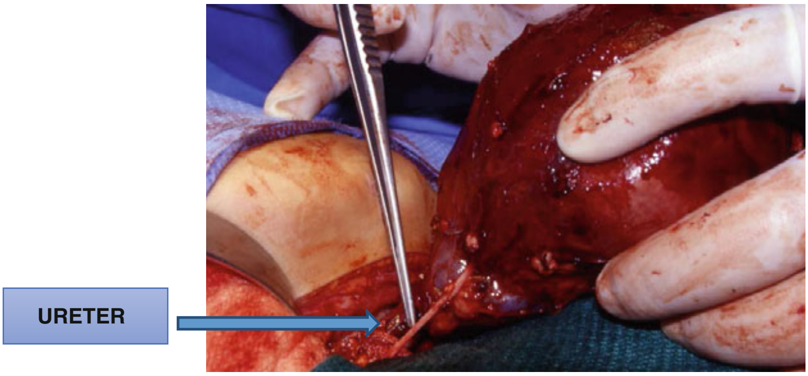


Fig. 4.67 A clinical intraoperative photograph showing radical nephrectomy for Wilms tumor. Note also the ureter which should be excised as low as possible

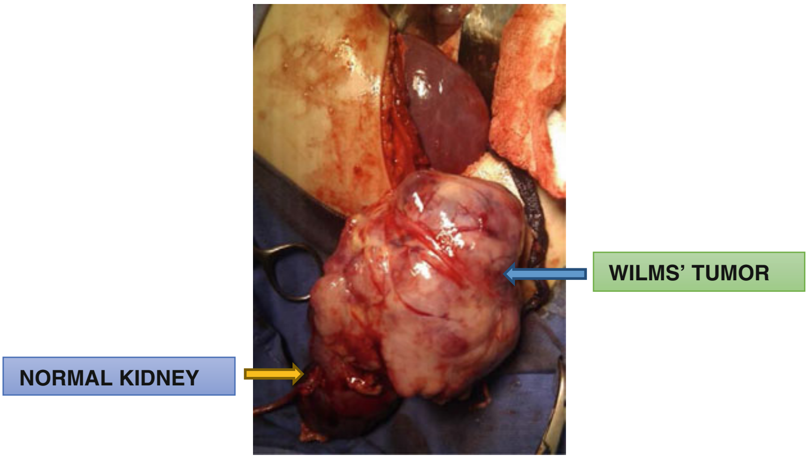


Fig. 4.68 A clinical intraoperative photograph showing radical nephrectomy for Wilms tumor

Stage and histology	Surgery	Chemotherapy	Radiotherapy
Stage I or II favorable histology without loss of heterozygosity (LOH) 1p and 16q	Nephrectomy	Vincristine, dactinomycin	No
Stage I or II favorable histology with LOH 1p and 16q	Nephrectomy	Vincristine, dactinomycin, doxorubicin	No
Stage III and IV favorable histology without LOH 1p and 16q	Nephrectomy	Vincristine, dactinomycin, doxorubicin	Yes
Stage III and IV favorable histology with LOH 1p and 16q	Nephrectomy	Doxorubicin, cyclophosphamide, etoposide	Yes

- Partial nephrectomy:
  - The role of partial nephrectomy remains controversial.
  - Partial nephrectomy may be feasible in only 10–15 % of patients, as most tumors are too large at initial diagnosis.
  - The main concern regarding a nephron-sparing procedure is that of local recurrence.
  - The NWTS-4 study showed an 8 % local recurrence rate following partial nephrectomy for patients with bilateral disease.
  - In the presence of bilateral Wilms' tumors, solitary kidney, or renal insufficiency, partial nephrectomy is a reasonable consideration.
- If inferior vena cava (IVC) thrombus is present, preoperative chemotherapy will reduce the cavotomy rate by 50 %.

Bilateral Wilms' tumor:

- With bilateral Wilms' tumor (6 % of cases), surgical exploration, biopsy of both sides, and accurate surgical staging (including lymph node biopsy of both sides) are performed.
- This is followed by 6 weeks of chemotherapy that is appropriate to the stage and histology of the tumor.
- Reassessment is then performed using imaging studies, followed by definitive surgery which can be any of the followings:
  - Unilateral radical nephrectomy and partial nephrectomy on the contralateral side.
  - Bilateral partial nephrectomy.
  - Unilateral nephrectomy only, if the response was complete on the opposite side. This approach dramatically

  reduces the renal failure rate following bilateral Wilms' tumor therapy.
- The overall 2-year survival rate is higher than 80 % with this approach, and the nephrectomy rate drops by 50 % in patients with bilateral Wilms' tumor.

4.2.11 Surgical Complications

- The overall surgical complication rate for Wilms' tumor is approximately 15–20 %.
- Surgical complications may include the following:
  - Small-bowel obstruction (7 %)
  - Hemorrhage (6 %)
  - Wound infection, hernia (4 %)
  - Vascular complications (2 %)
  - Splenic and intestinal injury (1.5 %)

Currently, Patients with High Risk Wilms' Tumor Are Treated as Follows

- Focal anaplastic stage I–III Wilms' tumors and diffuse anaplastic stage I Wilms' tumors:
  - Nephrectomy followed by vincristine, actinomycin-D, and doxorubicin in addition to local radiotherapy.
- Focal anaplastic stage IV Wilms' tumors and diffuse anaplastic stage II–III tumors:
  - Nephrectomy followed by chemotherapy including vincristine, actinomycin-D, doxorubicin, cyclophosphamide, etoposide, and carboplatin in addition to local radiotherapy
- Stage IV diffuse anaplastic Wilms' tumors:
  - More aggressive treatment is delivered; nephrectomy is followed by initial irinotecan and vincristine administration, which in turn is followed by actinomycin-D, doxorubicin, cyclophosphamide, carboplatin, etoposide, and radiotherapy.

4.2.12 Prognosis and Outcome

- The overall 5-year survival in children with Wilms' tumor is estimated to be approximately 90 %.
- This however is variable and the prognosis is highly dependent on the stage and treatment of tumor.
- Tumor-specific loss-of-heterozygosity (LOH) for chromosomes 1p and 16q identifies a subset of Wilms' tumor patients who have a significantly increased risk of relapse and death.
- LOH can now be used as an independent prognostic factor together with disease stage to give intensive treatment.
- Patients with synchronous bilateral tumors have a 70–80 % survival rate, whereas those with metachronous tumors have a 45–50 % survival rate.
- Patients with anaplastic Wilms' tumor have a worse prognosis compared with favorable histology Wilms' tumor. The 4-year overall survival rates are as follows:
  - Stage I: 83 %
  - Stage II: 83 %
  - Stage III: 65 %
  - Stage IV: 33 %
- Chemotherapy and radiation therapy can induce second malignant neoplasms.
  - Most secondary malignant neoplasms reported (e.g., bone tumors, breast and thyroid cancers) have occurred in irradiated areas. Nevertheless, certain chemotherapeutic agents, including doxorubicin, dactinomycin, and vincristine, may contribute to an increased risk for secondary malignancies.
- Bilateral, high-stage tumors with unfavorable histology are associated with a poor prognosis in spite of multimodal therapy.
- Children with Wilms' tumor have a minimal risk for impaired renal function but bilateral disease and radiotherapy can further compromise the renal function.
- Several cytotoxic agents may damage the liver of patients treated for Wilms' tumor, including dactinomycin and radiation induced hepatitis.

Overall Prognosis of Wilms' Tumor

- Stage I: 98 % 4-year survival; 85 % 4-year survival if anaplastic.
- Stage II: 96 % 4-year survival; 70 % 4-year survival if anaplastic.
- Stage III: 95 % 4-year survival; 56 % 4-year survival if anaplastic.
- Stage IV: 90 % 4-year survival; 17 % 4-year survival if anaplastic.
- Stage V: The 4-year survival was 94 % for those patients whose most advanced lesion was stage I or stage II; 76 % for those whose most advanced lesion was stage III.
- Patients with synchronous bilateral tumors have a 70–80 % survival rate whereas those with metachronous tumors have a 45–50 % survival rate.
- Patients with anaplastic Wilms' tumor have a worse prognosis compared with favorable histology Wilms' tumor; the 4-year overall survival rates are 83 %, 83 %, 65 % and 33 % for stages I, II, III, and IV, respectively.

- Patients with Wilms' tumor may develope hepatic veno-occlusive disease.
- Congestive heart failure is a well-known complication of the administration of anthracyclines.
- Radiation therapy can affect pulmonary function.
- Ovarian and testicular failures can follow whole-abdomen irradiation in childhood or alkylating agents.
- Radiation therapy may affect the growth.
- Relapse of Wilms' tumor:
  - The lungs are the most common site of relapse.
  - This site is affected in more than two thirds of children who have a relapse.
  - The tumor bed is the site of relapse only in about one fourth of patients.
  - The brain and the bones are not usual sites of relapse for Wilms' tumors with favorable histology.

4.2.13 Extrarenal Wilms' Tumors

- Extrarenal Wilms' tumor is extremely rare and occurs predominantly in children.
- The presence of an extrarenal Wilms' tumor excludes a primary tumor in the kidney.
- Most of the cases that have been reported involved the retroperitoneum.
- These tumors can occur in isolation or in association with other tumors usually teratomas.
- The diagnostic criteria necessary to establish the diagnosis include absence of primary kidney tumor and supernumery kidney.
- The origin of Wilms' tumor is controversial.
- There are hypotheses explaining the origin of extrarenal Wilm's tumor such as:
  - From ectopic metanephric blastema: This hypothesis is supported by the fact that the majority of these tumors occur in the retroperitoneal region. However the presence of extra-renal Wilms' tumor cephalad to kidney argues against it.
  - From primitive mesodermal tissue: This hypothesis is based on the occurrence of extrarenal Wilms' tumor in the cervix, vagina and inguinal canal, where there is a persistent mesonephric duct remnant.
  - Connheim's cell rest theory: This is a common hypothesis where cells with persistent embryonal potential undergo malignant transformation at any point of time.
- Reported location of Extrarenal Wilms' tumor include:
  - The retroperitoneum
  - Inguinal region
  - Endocervix, Uterus
  - Epididymis
  - Ovotestis
  - Vagina
  - Paraspinal
  - Paravesical
- The staging and management of extrarenal Wilms' tumor are similar to Renal Wilms' tumor.

4.3 Mesoblastic Nephroma

4.3.1 Introduction

- Mesoblastic nephroma is also called congenital mesoblastic nephroma (CMN) or fetal renal hamartoma.
- This tumor was first described as a separate entity by Bolande et al. in 1967.
- Prior to this, it was erroneously confused with congenital Wilms tumor.
- Congenital mesoblastic nephroma (or simply mesoblastic nephroma) represents 3–10 % of all pediatric renal tumors.
- It is called congenital because it can be diagnosed in utero by ultrasound or within the first 3 months of life.
- Approximately 50 % occur during the neonatal period and 80 % of cases are reported within the first month of life.
- Congenital mesoblastic nephroma represents 3–10 % of all pediatric renal tumors. It was initially confused with congenital Wilms' tumor.
- Mesoblastic nephroma is the most common renal tumor identified in the neonatal period and the most frequent benign renal tumor in childhood.
- Mesoblastic nephroma is most commonly diagnosed in the first 3 months of life.
- About 90 % present in the first year of life, 50–75 % of cases occur in young infants, and almost none occur after the age of 3 years.
- It is more common in males than females.
- The tumor is considered a hamartoma.
- It is presumed to originate from proliferating nephrogenic mesenchyme.
- Congenital mesoblastic nephroma is almost always unilateral and is rarely malignant.
- It may extend beyond the renal capsule, but rarely metastasizes to distant organs.
- Metastases to distant organs such as the brain, bone, and lungs have been reported.
- Commonly, mesoblastic nephroma appear as a large, solitary, predominantly solid, coarse, and echogenic renal mass that may contain cystic areas.
- Congenital renal tumors comprise 2.5–7 % of all perinatal tumors.
- Congenital renal neoplasms include, in decreasing order of frequency:
  - Congenital mesoblastic nephroma
  - Wilms tumor
  - Rhabdoid tumor of the kidney
  - Clear cell sarcoma
  - Hamartomas
  - Ossifying tumor of infancy
- The Diagnosis is usually made in the antenatal period or immediately after birth.
- Mesoblastic nephroma is considered generally a benign renal tumor.
- Among the renal tumors:
  - Wilms tumor is the most common renal tumor, accounting for 80–85 % of all pediatric renal tumors.
  - Congenital mesoblastic nephroma accounts for about 10–15 % of all pediatric renal tumors
  - Rhabdoid tumor of the kidney accounts for 5–10 % of all pediatric renal tumors.
  - Clear cell sarcoma (CCSK) accounts for 5–10 % of all pediatric renal tumors.
- The differential diagnosis based on age at presentation and includes the following tumors:
  - Mesoblastic nephroma: from birth to 1 year.
  - Rhabdoid tumor: from 1 to 2 years of age.
  - Clear cell sarcoma of the kidney: from 2 to 3 years of age.
  - Wilm's tumor: over 3 years of age (Mean 3.5 years).
- There is an association between CMN and:
  - Polyhyramnios with or without hydrops fetalis
  - Hypertension
  - Prematurity
  - Some mesoblastic nephromas are associated with paraneoplastic syndromes such as:
    - Hypertension: This is secondary to increased secretion of renin (hyperreninemia).
    - Hypercalcemia: This is due to prostaglandin secretion from the tumor cells.
- Congenital mesoblastic nephroma arises from renal mesenchyma and is usually benign.
- Although CMN is considered a benign tumor, it could behave aggressively.

- The tumor lacks renal blastema and neoplastic metanephric elements, thereby differentiating it from Wilms tumor.
- In addition, it tends to infiltrate the kidney, rather than form the pseudocapsule of classic Wilms tumor.
- Congenital mesoblastic nephroma is almost always unilateral.
- It may extend beyond the renal capsule, but rarely metastasizes to distant organs.

4.3.2 Classification

- Mesoblastic nephroma is a mesenchymal tumor.
- Macroscopically the tumor is a solid unencapsulated mass which often occurs near the renal hilum.
- It tends to invade the surrounding structures and renal parenchyma.
- Haemorrhage and necrosis are infrequent.
- Histologically, it is typically composed of connective tissue growing between nephrons, usually replacing most of the renal parenchyma.
- The classic cytological description of the lesion is that of cellular clusters of spindle cells, mild nuclear pleomorphism, mitotic activity and no blastema.
- Pathologically, mesoblastic nephroma are divided into two types:
  - The classic variant
  - The cellular variants
- The two types differ in the age at presentation, histologic characteristics, imaging characteristics and the biologic behavior of the tumors.
- The classic variant:
  - This presents earlier, usually before age 3 months.
  - It usually presents as a solid mass with small foci of necrosis or hemorrhage.
  - It does not invade the perinephric tissues or the vascular pedicle.
  - It is associated with an excellent outcome after complete surgical resection of the tumor.
  - On gross examination, the tumor:
    - Is noncapsulated
    - Has a whorled trabeculated appearance similar to leiomyomas, hence the name leiomyomatous hamartoma of the kidney.
  - Histologically:
    - It consists of uniform spindle cells arranged in bundles with scattered foci of entrapped normal glomeruli and tubules.
- The cellular variant:
  - This type presents later, usually after age 3 months.
  - More heterogeneous in appearance on imaging
  - Tends to be larger and presents later in infancy
  - May exhibit aggressive behavior including vascular encasement and metastasis
  - It demonstrates more aggressive imaging characteristics, with larger areas of necrosis and hemorrhage.
  - It may invade the perinephric fat and connective tissues.
  - It is associated with a higher rate of local recurrence and metastatic disease.
  - On gross examination:
    - The tumor is fleshy with multiple foci of necrosis, cystic change, and hemorrhage.
  - Histologically:
    - It consists of spindle cells arranged in a haphazard sheets with a limited tendency to form bundles as seen in the classic form.
  - The cellular variant may also demonstrate the t(12;15) translocation, which is diagnostic.
  - On reverse-transcription polymerase chain reaction (RT-PCR), it may demonstrate the *ETV6-NTRK3* gene fusion, a feature also seen in congenital infantile fibrosarcoma, hence the name infantile fibrosarcoma of the kidney.
- Factors that increase the risk of recurrence and metastasis include:
  - Cellular variant
  - Older age at presentation
  - Positive surgical resection margins
- Metastases to distant organs such as the brain,

bone, and lungs have been reported. These are seen in cellular variant.

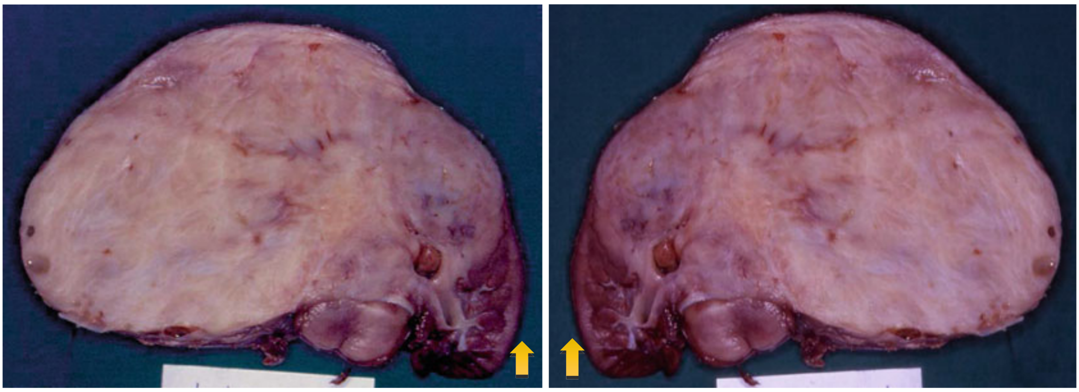
- The cellular variant has been shown to bear the t(12;15)(p13;q25) and ETV6 (chromosome 12)-NTRK3 (chromosome 15) gene fusion. These combined genes are thought to activate tyrosine kinase growth signaling. This gene fusion transcript is also reported in congenital or infantile fibrosarcoma

4.3.3 Epidemiology

- Mesoblastic nephroma is the most common renal tumor in neonates and infants and represents 3–10 % of the pediatric renal tumors.
- Mesoblastic nephroma is the most common renal tumor presenting in the neonatal period and accounts for approximately 54 % of tumors in this age group.
- It was initially described as a benign tumor, but currently a spectrum of mesoblastic nephroma exists:
  - The classic type representing the benign disease
  - The cellular variant representing the aggressive disease (40–60 %)
  - The mixed tumors falling somewhere in the middle.
  - Mesoblastic nephroma has a slight male predominance, with a male-to-female ratio of 1.5:1.
  - Histologically, the classic form is characterized by rare mitoses and absence of necrosis. Entrapped tubules and/or glomeruli are usually seen at the periphery of the tumor.
  - Atypical or cellular variant is characterized by a high mitotic index, hypercellularity, and an atypical growth pattern with necrosis, hemorrhage, and invasion of adjacent structures.

4.3.4 Histopathology (Figs. 4.69 and 4.70)

- Mesoblastic nephroma is a solid tumor and mostly these tumors are located near the hilum of the kidney and may extensively involve the renal sinus.
- Cysts are rarely seen but there may be hemorrhage and necrosis.
- The tumor is usually well circumscribed, but it may be seen infiltrating the renal parenchyma and even the perirenal fat.
- The cut surface of the tumor specimen shows a yellow-tan tumor with a "whorled" appearance that is similar to a uterine leiomyoma with spindled cell bundles.
- It is composed of immature renal stromal cells.
- The tumor lacks renal blastema and neoplastic metanephric elements, thereby differentiating it from Wilms tumor.



Figs. 4.69 and 4.70 Clinical photograph of a resected mesoblastic nephroma. Note the whorled appearance of the tumor. Note also the normal kidney tissue. Note that the normal kidney is infiltrated by the tumor and not compressed like Wilms' tumor. Note also the absence of a capsule

- The tumor tends to infiltrate the kidney, rather than form the pseudocapsule of classic Wilms tumor.
- There are two pathologic variants of mesoblastic nephroma:
  - Classic
  - Atypical or cellular.
- The classic type is characterized by rare mitoses and absence of necrosis. Entrapped tubules and/or glomeruli are usually seen at the periphery of the tumor.
- Classic mesoplastic nephroma:
  - Fascicles and whorls of spindly cells.
  - These cells have the features of secondary mesenchyme, which, in contrast with those of primary mesenchyme (mesoblast), lack the capacity to form epithelial structures.
  - Instead, the proliferating cells acquire the features of fibroblasts, myofibroblasts, or smooth muscle cells.
  - These cells contain vimentin, fibronectin, and sometimes actin, but not keratin or laminin.
  - The tumor has irregular borders, with bands of tumor extending into surrounding soft tissue.
  - It also permeates the adjacent renal parenchyma to encircle groups of tubules and glomeruli.
  - Metaplastic tissues are usually found at the tumor-kidney interface or near entrapped renal tubules and glomeruli, most commonly cartilage.
  - Extramedullary hematopoiesis and cuboidal metaplasia may also be present.
  - Mitotic figures may be encountered, but frequent mitoses are more characteristically seen in cellular mesoblastic nephroma.
- Atypical or cellular variant is characterized by:
  - A high mitotic index.
  - Hypercellularity.
  - An atypical growth pattern with necrosis, hemorrhage, and invasion of adjacent structures.
  - The cellular type accounts for 40–60 % of mesoblastic nephroma cases.
- Cellular mesoblastic nephroma:
  - This is more cellular than the classical type and has a sarcomatous appearance consisting of tightly packed cells with frequent mitoses (25–30/10 HPF).
  - Data from the National Wilms Tumor Study show that cellular mesoblastic nephroma is commoner than classic mesoblastic nephroma with a ratio of 3:1.
  - Cellular mesoblastic nephroma presents a few months later in life than the classic mesoblastic nephroma.
  - Unlike the classic type, cellular mesoblastic nephroma may reach a huge size and can weigh more than 1 kg (Fig. 4.71).

– Histologically, two types of cells are seen. The more common cell type is a plump cell with ample cytoplasm and a vesicular nucleus. The less common type is a blue cell, which shows less cytoplasm and resembles cells of infantile fibrosarcoma.

- The cellular variant has been shown to bear the t (12; 15) (p13; q25) and ETV6 (chromosome 12)-NTRK3 (chromosome 15) gene fusion. These combined genes are thought to activate tyrosine kinase growth signaling. This gene fusion transcript is also reported in congenital or infantile fibrosarcoma.

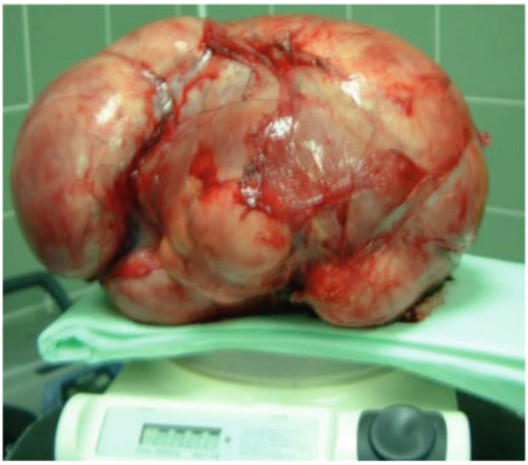
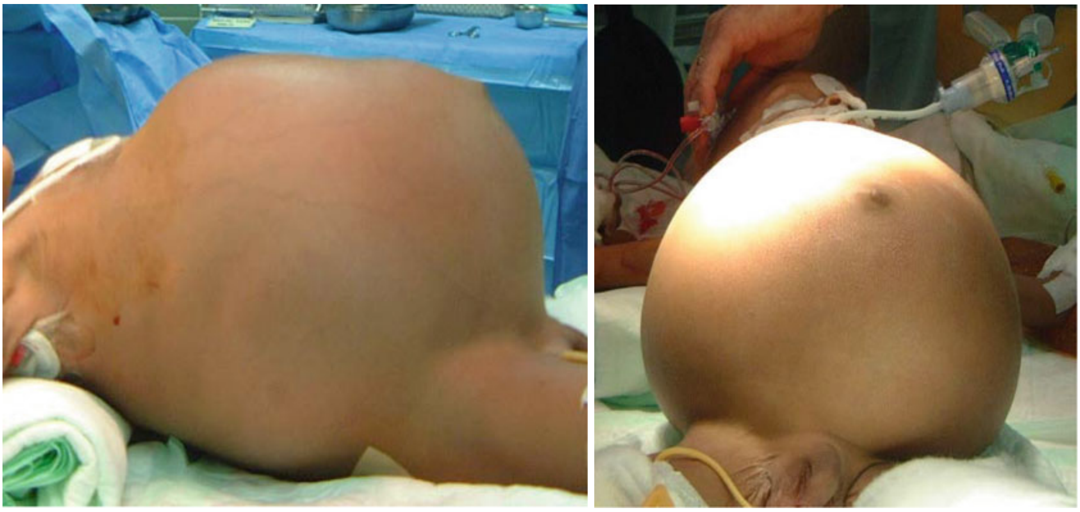


Fig. 4.71 A clinical photograph showing an excised large mesoblastic nephroma that weighed more than one kilogram

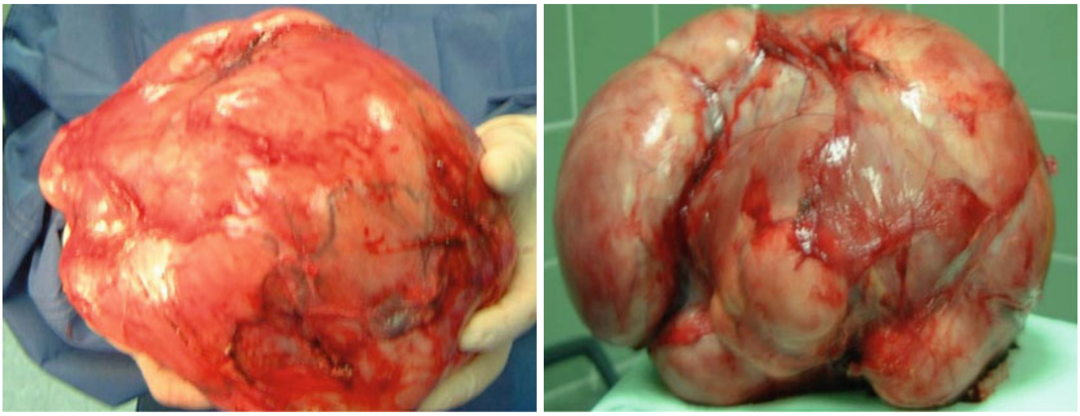
- Factors that increase the risk of recurrence and metastasis include:
  - Cellular variant.
  - Older age at presentation.
  - Positive surgical margins.
- Metastases to distant organs such as the brain, bone, and lungs have been reported with the cellular type.
- There is also a variant of mesoblastic nephroma which is cystic. This is called cystic mesoblastic nephroma which can be confused with other congenital cystic lesions of the kidney.

4.3.5 Clinical Features

- The diagnosis of mesoblastic nephroma may be made antenatally on ultrasound performed as early as 18–20 weeks' gestation.
- Fetal ultrasonography is useful in differentiating a renal mass from hydronephrosis but if the mass is large it may be difficult to determine the origin of the tumor.
- Fetal magnetic resonance imaging (MRI) may be more helpful in determining the organ of origin because of the ability to take images in multiple planes.
- Prematurity and polyhyramnios with or without hydrops fetalis are known to be associated with mesoblastic nephroma.
- Postnatally, although abdominal ultrasound and CT-scan are useful in diagnosing mesoblastic nephroma, MRI is the most accurate imaging modality, as it most accurately depicts the local and regional extent of the tumor.
- These radiological investigations although they may suggest the most likely diagnosis but cannot definitively differentiate a mesoblastic nephroma from other renal tumors and histologic examination is the only definitive diagnosis.
- Polyhydramnios is reported in 71 % of pregnancies associated with mesoblastic nephroma.
- The most common clinical presentation is an asymptomatic abdominal mass.
- The mass can grow rapidly and attain a large size (Figs. 4.72, 4.73, 4.74, and 4.75).
- Hematuria is a rare manifestation of mesoblastic nephroma.
- Paraneoplastic syndromes such as hypertension or hypercalcemia may be present.
- Hypertension is thought to be secondary to increased renin production by the trapped glomeruli in the tumor.
- Hypercalcemia: This is due to prostaglandin secretion from the tumor cells.



Figs. 4.72 and 4.73 Clinical photographs showing marked abdominal distension secondary to a very large mesoblastic nephroma



Figs. 4.74 and 4.75 Clinical photographs of a very large mesoblastic nephroma that was completely excised. In spite of the large size there were no secondaries

- Potential intrauterine complications with large mesoblastic nephroma:
  - Abdominal dystocia at birth
  - Arterio-venous shunting with subsequent development of hydrops fetalis.

4.3.6 Investigations

- Complete blood count
- Serum electrolyte, BUN and creatinine
- Live function tests
- Plain radiograph: This may demonstrate a soft tissue mass displacing bowel. Calcification is very rarely seen (Figs. 4.76).
- Abdominal Ultrasound:
  - This reveals a well-defined mass with low-level homogeneous echoes.
  - The presence of concentric echogenic and hypoechoic rings can be a helpful diagnostic feature.
  - A more complex pattern due to hemorrhage, cyst formation and necrosis can also be seen and tends to favor the cellular variant.
  - Color Doppler ultrasound may show increased vascularity.
  - Antenatal ultrasound may also show evidence of associated polyhydramnios.
- Abdominal CT-scan (Figs. 4.77 and 4.78):
- This shows a solid hypoattenuating renal lesion with variable contrast enhancement.
- Cystic areas, necrosis, and hemorrhage are uncommon but can be seen in the cellular variant.

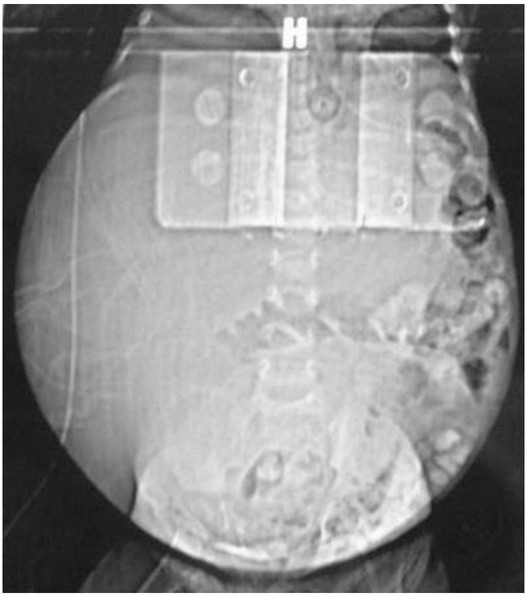
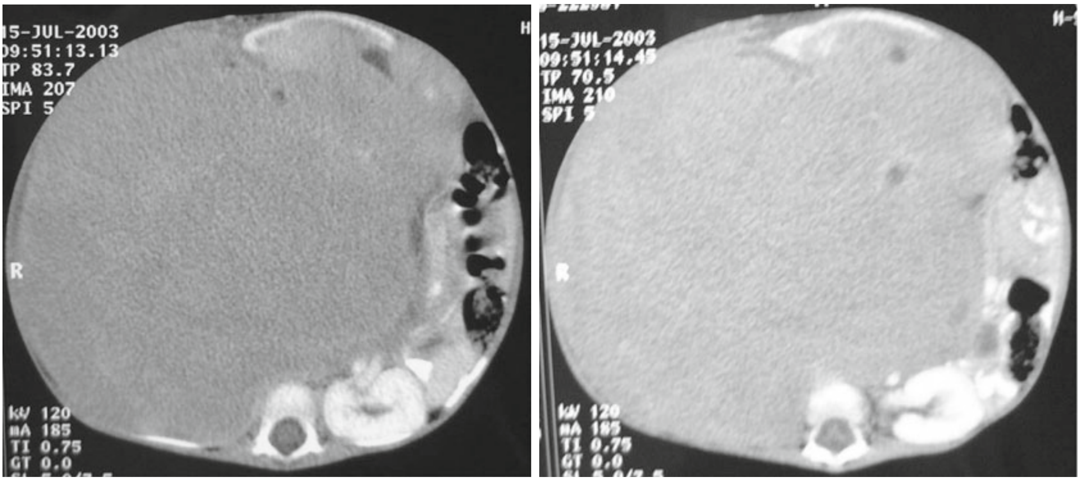


Fig. 4.76 Plain x-ray showing a large soft tissue density occupying almost the whole abdomen

- Abdominal MRI:
  - Antenatal abdominal MRI is the most useful investigation to assess and diagnose mesoblastic nephroma. This reveals a homogenous hypointense renal mass.



Figs. 4.77 and 4.78 Abdominal CT-scan showing a very large right side renal tumor. This was excised and found to be mesoblatic nephroma. Note the normal looking left kidney

  - Postnatal MRI is also useful in outlining the site and size of the tumor properly as well as its relation to other intra-abdominal organs.

4.3.7 Treatment and Prognosis

- The majority of these tumors are benign tumors and have a favorable outcome.
- The cellular variant can at times be aggressive.
- Surgical resection of congenital mesoblastic nephroma is the treatment of choice and this is curative.
- Most cases of mesoblastic nephroma are clinically benign. However, there are reports of local recurrence in incompletely resected tumors, and metastases to the brain, lung, heart and bone.
  - In such cases, patients may be treated with chemotherapy and/or radiation therapy.
- When diagnosed in the first 7 months of life, the 5-year event-free survival rate is 94 % and the overall survival rate is 96 %.
- Patients at increased risk of recurrence and/or metastasis are those showing incomplete resection with positive resection margins, cellular type, and age at diagnosis of more than 3 months

4.4 Clear Cell Sarcoma of the Kidney (CCSK)

4.4.1 Introduction

- In the past, clear cell sarcoma of the kidney was considered as a subtype of Wilms' tumor.
- Clear cell sarcoma is now considered a distinct clinical and histologic entity.
- In 1970, Kidd initially recognized clear cell sarcoma of the kidney as a distinct clinicopathologic entity, noting its propensity to metastasize to bone.
- The distinctive histopathologic features of clear cell sarcoma of the kidney were reported simultaneously in 1978 by Morgan and Kidd, Marsden et al, and Beckwith and Palmer.
- Clear cell sarcoma of the kidney is also known as bone metastasizing renal tumor of childhood because of its tendency to metastasize to bones.
- Clear cell sarcoma of the kidney (CCSK), is an uncommon renal tumor of childhood.
- It accounts for 4–5 % of all primary renal tumors in childhood.
- Approximately 20 new cases are diagnosed each year in the United States.
- It is difficult to differentiate clear cell sarcoma from Wilms' tumors both clinically and radiologically.

- Age of presentation of CCSK ranges from 2 months to 14 years, with a mean age at diagnosis of 36 months.
- Clear cell sarcoma of the kidney is extremely rare in infants younger than 6 months old.
- The highest incidence (50 % of the cases) of clear cell sarcoma of the kidney is in children aged 2–3 years.
- It occurs more in males than females, with a male-to-female ratio of 2.04:1.
- CCSK arises from a renal mesenchymal cell that possesses neural markers.
- Grossly, the tumor is soft and well circumscribed.
- Histologic analysis show small cells with inconspicuous nucleoli and ill-defined cell membranes and a prominent capillary network.
- The Clinical presentation includes abdominal pain, hypertension, and hematuria.
- Radiologically, it is difficult to differentiate this from Wilms tumor but a sharply demarcated solid intrarenal mass without intra-vascular extension is most radiological finding.
- Clear cell sarcoma of the kidney is characterized by:
  - Its propensity to metastasize to bones.
  - Poor prognosis.
  - The sarcomatous nonepithelial nature.
  - CCSK may also recur many years after its initial diagnosis.
- The tumor is characterized by its aggressive behavior and is associated with a higher rate of relapse and mortality than Wilms tumor. It may metastasize to the bones, lymph nodes, brain, liver, and lungs, in some cases long after nephrectomy.
- CCSK is an aggressive renal tumor with a unique propensity to metastasize to bone and brain, as well as lung and abdomen.
- Only 4–5 % of patients with CCSK present with distant metastases.
- The most common site of metastasis at the time of presentation in patients with clear cell sarcoma of the kidney is the ipsilateral renal hilar lymph nodes.
- Bone is the most common site of distant metastases (15 %).
- This is followed by the lungs, abdomen, retroperitoneum, brain, and liver.
- Unusual soft tissue sites (scalp, epidural, nasopharynx, neck, paraspinal, ovary, abdominal wall, and axilla) and other sites (orbit) have also been reported.
- Since bone metastases may occur with this disease, bone scintigraphy or FDG-PET scan is recommended and Brain CT scan or MRI are part of the workup of these patients.
- Overall, the prognosis of clear cell sarcoma is poor when compared with that of patients with Wilms' tumors.
- The treatment consists of radical nephrectomy, chemotherapy, and radiotherapy.
- The prognosis of CCSK is generally poor, but the development of newer treatment regimens has improved survival and currently the relapse-free and cancer-specific survival rate for revised stage 1 CCSK is about 90–100 %.
- Currently, the overall survival rate for patients with CCSK is about 83 %.

4.4.2 Pathophysiology

- Clear cell sarcoma of the kidney originates from renal mesenchymal cells with neural markers.
- It is not associated with intralobar nephrogenic rests.
- CCSK is usually unilateral affecting only one kidney and no bilateral cases have been reported.
- At the time of presentation:
  - 25 % of patients presented with stage I tumors
  - 37 % of patients presented with stage II tumors
  - 34 % of patients presented with stage III tumors
  - 4 % of patients presented with distant metastases
- The most common site of metastasis at the time of presentation in patients with clear cell sarcoma of the kidney is the ipsilateral renal hilar lymph nodes.
- Skip metastases to periaortic lymph nodes have been reported in patients with clear cell sarcoma of the kidney.

- Bone is the most common site of metastases (15 %), followed closely by lung, abdomen, retroperitoneum, brain, and liver.
- Unusual soft tissue sites (scalp, epidural, nasopharynx, neck, paraspinal, ovary, abdominal wall, and axilla) and other sites (orbit) have been reported.
- Approximately 20 % of documented clear cell sarcoma of the kidney metastases occurred at least 3 years after diagnosis; some occurred as long as 10 years later.

4.4.3 Clinical Features

- The clinical manifestations of patients with clear cell sarcoma of the kidney (CCSK) are similar to those patients with Wilms tumor.
- The usual presentation is with an abdominal mass that was noticed by the parents or primary care physician or pediatrician. Sometimes, the mass is discovered accidently during an abdominal ultrasound that was ordered for something else. The mass may be discovered by the mother while dressing or giving bath to the child.
- Other clinical presentations include:
  - Abdominal pain
  - Gross or microscopic hematuria
  - Fever
  - Hypertension
- Clinically, the patient has a large palpable unilateral abdominal mass.
- No specific chromosomal translocation or syndromes have been associated with clear cell sarcoma of the kidney.
- The proto-oncogene c-kit is overexpressed in clear cell sarcoma of the kidney but is not accompanied by gene amplification or activating mutations.
- The t(10;17)(q22;p13) and deletion 14q have been described.

4.4.4 Investigations

- CBC
- Serum electrolytes, BUN and creatinine levels
- Liver function testes
- Prothrombin time and activated partial thromboplastin time
- Abdominal ultrasound:
  - This is important to define the tumor, its origin and extent.
  - It is also important to evaluate the status of the inferior vena cava and any gross extension into the renal vein.
  - Tumor thrombus in the renal vein is present in approximately 5 % of patients with clear cell sarcoma of the kidney.
- CT scans of the chest and abdomen:
  - To define the origin and extent of the tumor
  - To define secondaries in the lymph nodes, liver and lugs
- Bone scan is important to exclude secondaries
- Brain CT scan or MRI are also important to detect secondaries

4.4.5 Histopathology

- Clear cell sarcoma of the kidney usually presents as a large mass markedly distorting or almost completely replacing the kidney.
- The tumor can reach a large size with a mean tumor diameter of 11.3 cm (2.3–24 cm).
- The mean weight of the kidney tumor is about 661 g.
- CCSK is an epicenteric tumor and the renal medulla is the most common location.
- No case of multicentric tumor was identified.
- On cut sections of the tumor:
  - It appears as tan-gray, soft, and mucoid.
  - There are multiple cystic areas and sometimes these cysts represent the dominant feature.
  - Discrete foci of necrosis and hemorrhage may be present.
- Histologically, clear cell sarcoma of the kidney shows three components:
  - Cord cells:
    - These are small round-to-oval cells with deceptively bland cytologic features, including mitotic figures.

  - Septal cells:
    - These are spindle-shaped cells along the fibrovascular septa (fibrovascular septa can be demonstrated more convincingly using reticulum stain).
  - An intercellular matrix:
    - This is composed of mucopolysaccharide, which ranges from minute indiscernible droplets to large pools imparting the clear appearance of clear cell sarcoma of the kidney.
- Depending on the amount, distribution, and variation in morphology of the 3 components, CCSK is divided histologically into two types:
  - Classic clear cell sarcoma of the kidney
  - Variant clear cell sarcoma of the kidney
  - The classic pattern usually represents the predominant pattern in most clear cell sarcoma of the kidney tumors.
  - The classic histologic pattern is characterized by cord cells arranged in cords, nests, or groups surrounded by thin fibrovascular septa. A moderate amount of clear intercellular matrix separates the cord cells, giving a clear appearance, hence the designation clear cell sarcoma of the kidney.
  - The most common variant is the myxoid CCSK.
  - The variant patterns include:
    - Myxoid pattern (50 %)
    - Sclerosing pattern (35 %)
    - Cellular pattern (26 %)
    - Epithelioid pattern (trabecular or acinar type) (13 %)
    - Palisading (Verocay body) pattern (11 %)
    - Spindle cell pattern (7 %)
    - Storiform pattern (4 %)
    - Anaplastic pattern (2.6 %)
  - The anaplastic pattern is defined by nuclear hyperchromasia, nuclear gigantism, and atypical mitoses.
  - Overexpression of p53 (>75 % of the nuclei) has been demonstrated in anaplastic clear cell sarcoma of the kidney.
  - The tumor cells usually test positive for vimentin and negative for cytokeratin, factor VIII–associated antigen, epithelial membrane antigen, desmin, S100, factor XIIIa, c-kit, polyclonal carcinoembryonic antigen (CEA), and MAC387.
  - Positive staining results for cytokeratin, α_1-antitrypsin, and α_1-antichymotrypsin have also been described.

4.4.6 Treatment

- The overall survival of children with clear cell sarcoma of the kidney remains considerably lower than that of patients with favorable-histology Wilms tumor.
- The overall survival has improved for patients with clear cell sarcoma of the kidney from NWTS-3 to NWTS-4 (83 % vs 66.9 % at 8 year).
- This is attributed to the use of chemotherapy for prolonged periods.
- NWTS-4 showed that patients treated with vincristine, doxorubicin, and dactinomycin for 15 months had an improved relapse-free survival rate compared with patients treated for 6 months (87.5 % vs 60.6 % at 8 year).
- The 8-year relapse-free survival rate for localized clear cell sarcoma of the kidney stages I–III is 88 %, but late relapses have been reported.
- In the NWTS-5 protocol, patients with all stages of CCSK are treated with the same regimen used in patients who have Wilms tumor with diffuse anaplasia (excluding stage I).
- This treatment consists of:
  - A radical nephrectomy
  - Followed by chemotherapy with cyclophosphamide, etoposide, vincristine, and doxorubicin for 24 weeks.
  - And radiotherapy
  - CCSK commonly responds poorly to treatment with vincristine and actinomycin alone, but the addition of doxorubicin to chemotherapy regimens has improved survival rates.
- In the current Children's Oncology Group protocol (AREN0321), all patients with clear cell sarcoma of the kidney, except patients with stage IV, continue treatment as in NWTS-5.

- Patients with stage I who undergo lymph node sampling do not undergo radiation therapy to the tumor bed.
- Any patient with stage I who has not undergone lymph node sampling is upstaged to stage II.
- Patients with stage IV undergo treatment with irinotecan and vincristine in an upfront window approach before treatment with cyclophosphamide, etoposide, vincristine, doxorubicin, and cyclophosphamide.
- Surgical treatment:
  - Radical nephrectomy is the initial treatment of choice if the lesion is resectable.
  - If the tumor is not resectable, a biopsy is performed, and chemotherapy is administered, followed by surgical resection after a response has been obtained.
  - Patients with clear cell sarcoma of the kidney (CCSK) are treated with combination chemotherapy.
  - The addition of doxorubicin to chemotherapeutic regimens has been shown to improve disease-free survival rates.
- After completing chemotherapy, patients should continue to have regular follow up with blood and radiographic evaluations on an outpatient basis.
- The follow up should be every 1–3 months for the first year, every 3–6 months for the second and third years, then yearly thereafter.
- There is an increase in number of CNS recurrences of clear cell sarcoma of the kidney (CCSK) which should be taken in consideration during follow ups.
- Clear cell sarcoma of the kidney tumors are associated with late recurrence; the most common site of recurrence is the brain and then the lung.
- The patients remain at risk for recurrence after 2 years posttherapy. Tumors may recur as long as 10 years after completion of treatment.
- Treatment of patients with recurrent clear cell sarcoma of the kidney:
  - This depends on the initial chemotherapy.
  - Cyclophosphamide and carboplatin should be considered if not used initially.
  - Patients with recurrent clear cell sarcoma of the kidney that involves the brain can be treated with ifosfamide, carboplatin, and etoposide (ICE), coupled with local control consisting of either surgical resection and/or radiation.
- Patients require follow-up evaluation for toxic effects resulting from chemotherapy, radiotherapy, or both. These include:
  - Cardiomyopathy
  - Patients are at risk for renal failure because they have a single kidney
  - Radiation effects including asymmetry of the back muscles
  - Secondary malignant neoplasms
  - Infertility
  - Risk of intestinal obstruction

4.4.7 Prognosis

- The prognosis for CCSK has improved with the addition of doxorubicin to chemotherapy regimens with a 66 % reduction in overall mortality.
- This is particularly so for low stage tumors,
- The reported stage-dependent 6-year survival is:
  - 97 % for stage I tumors.
  - 75 % for stage II tumors.
  - 77 % for stage III tumors.
  - 50 % for stage IV tumors.
- Twenty-nine percent of patients with CCSK have lymph node metastases at the time of diagnosis, and bone metastasis is the most common form of relapse.
- Metastatic lesions have also been reported in the liver, brain, soft tissue sites, and lung with more unusual metastases to the skeletal muscles, testis, and salivary gland.
- Approximately 20 % of documented clear cell sarcoma of the kidney metastases occurred at least 3 years after initial diagnosis; bur relapses of CCSK as many as 10 years after original diagnosis have been reported.

4.5 Malignant Rhabdoid Tumor of the Kidney

4.5.1 Introduction

- Malignant rhabdoid tumor (MRT) is a rare and very aggressive renal tumor that occurs mainly in children.
- The term *rhabdoid* was used due to its similarity with rhabdomyosarcoma. The tumor cells resemble muscle cells under the light microscope.
- It was originally described as a variant of Wilms' tumor.
- Malignant rhabdoid tumor was initially described in 1978 as a rhabdomyosarcomatoid variant of a Wilms tumor because of its occurrence in the kidney and because of the resemblance of its cells to rhabdomyoblasts.
- The absence of muscular differentiation led Haas and colleagues to coin the term rhabdoid tumor of the kidney in 1981.
- It is now recognized as an entity separate from a Wilms tumor.
- In contrast to a Wilms tumor, a malignant rhabdoid tumor of the kidney is characterized by the early onset of local and distant metastases and resistance to chemotherapy.
- Malignant rhabdoid tumor of the kidney is a highly aggressive, has a poor prognosis, and tend to occur in children less than 2 years of age.
- Malignant rhabdoid tumor of the kidney is a rare, highly aggressive malignancy of early childhood and accounts for approximately 2 % of pediatric renal malignancies.
- Malignant rhabdoid tumors of the kidneys are more common in infants.
- Most patients with malignant rhabdoid tumor of the kidney are younger than 2 years of age at presentation.
- The median age at diagnosis is 10.6 months, with a mean age of 15 months.
- The majority are diagnosed between 6 and 12 months of age.
- It occurs exclusively in children, with 60 % occurring before the age of 1 year of age, and 80 % before the age of 2 years.
- The age at presentation of malignant rhabdoid tumor of the kidney overlaps with that noted for congenital mesoblastic nephroma.
- It is more common in males with a male to female ratio of 1.5:1.
- Clinically, patients may develop hypercalcemia secondary to elevated parathormone levels.
- Rhabdoid tumor has the worst prognosis of all renal tumors. It is highly aggressive and metastasizes early, with most patients presenting with advanced disease.
- Eighty percent develop metastases, most commonly to the lungs and less often to the liver, abdomen, brain, lymph nodes, or skeleton.
- Survival is poor, with an 18-month survival rate of only 20 %.
- A key to the diagnosis is negativity of immunohistochemistry for SWI/SNF-related, matrix-associated, actin-dependent regulator of chromatin, sub-family B, member 1 INI1 (SMARCB1).
- There is no standard treatment for MRT and prognosis is very poor with published overall survivals of 15–36 %, however more recent treatment regimens including surgery, radiotherapy, high dose chemotherapy and autologous stem cell rescue (HDCT/ASCR) may improve survival.
- Malignant rhabdoid tumors occur at other sites outside the kidney including:
  - The liver
  - Soft tissues
  - Lung
  - Skin
  - Heart
  - The central nervous system
  - The cerebellum is the most common location for primary intracerebral MRT
- Abnormalities in chromosome 22 (commonly deletions of the INI1 gene in chromosome 22) are commonly seen in patients with MRT.
- About 10–15 % of patients with MRTs have synchronous or metachronous brain tumors, many of which are second primary malignant rhabdoid tumors.
- The brain tumors may precede or appear several years after the detection of malignant rhabdoid tumor of the kidney.

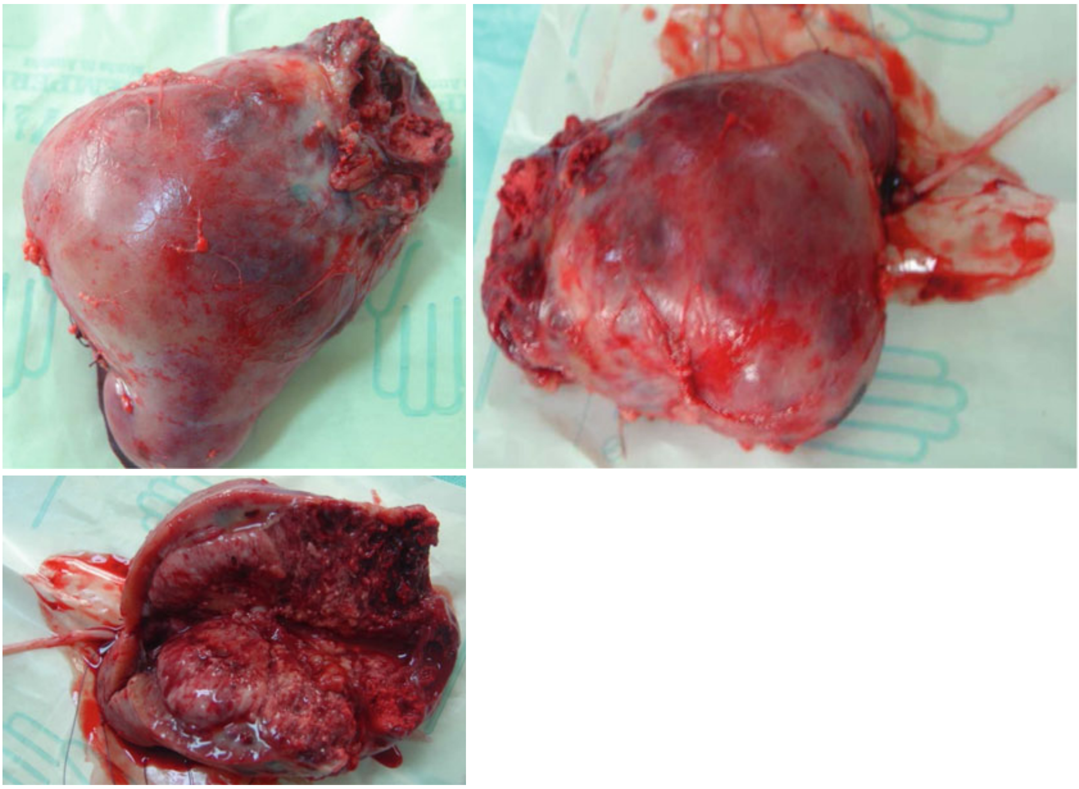
- For this reason, brain MRI is part of the workup of these patients and a close follow-up is also important in these patients.
- Malignant rhabdoid tumor of the kidney can be diagnosed in utero.
- The presentation of these patients include:
  - An abdominal mass
  - Hypertension
  - Hypercalcemia
  - Fever
  - Hematuria
- The clinical and radiological images characteristics of malignant rhabdoid tumors of the kidney are similar to those of congenital mesoblastic nephroma, clear cell sarcoma of the kidney, and Wilms' tumor.
- Whereas the overall survival rate for Wilms tumors exceeds 85 %, the survival rate for renal malignant rhabdoid tumors is only 20–25 %.

4.5.2 Etiology and Pathophysiology

- Malignant rhabdoid tumors frequently contain deletions at chromosome locus 22q11.1.
- This locus contains the *SWI/SNF* related, matrix-associated, actin-dependent regulator of chromatin, subfamily B, member 1 (*SMARCB1*) gene.
- *SMARCB1* encodes a member of the human *SWI/SNF* complex.
- *SMARCB1* is presumed to function as a classic tumor suppressor and the primary gene responsible for malignant rhabdoid tumor development.
- CNS atypical teratoid/rhabdoid tumors (AT/RT) have deletions of the *SMARCB1* gene.
- This suggests that rhabdoid tumors of the kidney and brain are identical or closely related entities.
- Moreover, 10–15 % of patients with malignant rhabdoid tumors have synchronous or metachronous brain tumors, many of which are second primary malignant rhabdoid tumors.
- Germline *SMARCB1* mutations were detected in some of these patients.
- This is estimated to occur in approximately 15–30 % of patients with malignant rhabdoid tumor.
- Although mutations or deletions of the *SMARCB1/INI1* gene play a role in the development of malignant rhabdoid tumor, the triggering mechanisms for these genetic alterations are unknown.
- Several cases of familial malignant rhabdoid tumor were also reported.
- No environmental or infectious associations with malignant rhabdoid tumor have been established.

4.5.3 Histologic Findings

- Grossly, malignant rhabdoid tumor of the kidney are heterogeneous, bulky, lobulated, friable, solid, gray-tan masses with areas of necrosis and hemorrhage (Figs. 4.79, 4.80, and 4.81).
- On microscopic examination, malignant rhabdoid tumors are characterized by the followings:
  - Sheets or solid trabeculae of tumor cells.
  - The tumor cells are large with vesicular nuclei, prominent cherry-red nucleoli.
  - The tumor cells are characterized by an abundant eosinophilic cytoplasm.
  - Many tumor cells have a distinct, pale or hyaline pink intracytoplasmic rhabdoid inclusion in the cytoplasm.
  - Mitoses are frequent and necrosis is common.
  - A subset of tumors may be composed predominantly of primitive undifferentiated small round blue cells.
  - Other patterns described as sclerosing (including chondroid), epithelioid, spindled, lymphomatoid or histiocytoid, and vascular may coexist with the classic pattern.
  - Malignant rhabdoid tumor of the kidney typically has an infiltrative border with the surrounding nonneoplastic cortex and renal medulla.
- The most useful ultrastructural findings include:
  - A large whorl of intermediate filaments in the cytoplasm with a diameter of 8–10 nm.
  - Dilated rough endoplasmic reticulum



Figs. 4.79, 4.80, and 4.81 Clinical operative photographs showing nephrectomy for malignant rhabdoid tumor of the kidney. Note the tumor is lobulated, friable, with areas of necrosis and hemorrhage

- Rudimentary cell junctions
- Cytoplasmic tonofilamentlike bundles
- Immunohistochemical examination: The tumor cells are polyphenotypic with consistent staining for vimentin.
- The tumor cells are positive for epithelial membrane antigen and/or cytokeratin.
- The tumor cells are positive for glial fibrillary acidic protein, neuron-specific enolase, smooth muscle actin, desmin, and CD99.
- Malignant rhabdoid tumor lacks *INI1* immunohistochemical staining.

4.5.4 Clinical Features

- Malignant rhabdoid tumor is a rare tumor.
- It accounts for about 1.6 % of all childhood renal tumors.
- Malignant rhabdoid tumor occurs slightly more frequently in males than in females, with male-to-female ratio of 1.4:1.
- The median age at presentation is 10.6 months, with a mean age of 15 months.
- Most patients are younger than 2 years at presentation.
- The usual presentation is an abdominal mass but the initial manifestation may be due to metastatic disease.
- It is highly aggressive and metastasizes early, with up to 80 % of patients presenting with metastatic disease, typically to the lungs and less often to the liver, abdomen, brain, lymph nodes, or skeleton.
- The mass may be noticed by the parents usually during clothing or while giving a bath to the child.
- Sometimes, the mass is discovered by the primary care physician or pediatrician.

- The mass may reach a large in size.
- Sometimes they present with pain or more commonly fussiness.
- Gross hematuria is a presenting feature in approximately 60 % of patients.
- This is in contrast to patients with Wilms tumor where only 20 % of patients have gross hematuria.
- Fever is a presenting symptom in 50 % of patients
- This is in contrast to patients with Wilms tumor where only 25 % of patients have fever.
- As many as 20 % of patients with a rhabdoid tumor of the kidney have synchronous or metachronous CNS tumors, including both metastases and second primary cancers.
- Hypertension is observed in up to 70 % of patients.
- There may be evidence of focal neurologic signs or increased intracranial pressure in light of the prevalence of synchronous CNS tumors.

4.5.5 Investigations and Diagnosis

- The definitive diagnosis of malignant rhabdoid tumor (MRT) is by means of histologic analysis.
- CBC count:
  - Approximately 55 % of patients with malignant rhabdoid tumor present with a hemoglobin level of less than 9 g/dL.
  - Only 25 % of patients with Wilms tumor are anemic at presentation.
- Urinalysis:
  - Microscopic hematuria is seen in 75 % of patients with malignant rhabdoid tumor.
  - Approximately 25 % of patients with malignant rhabdoid tumors have proteinuria.
- Serum calcium measurement:
  - As many as 25 % of patients with malignant rhabdoid tumor present with hypercalcemia.
  - This finding is attributed to the ectopic production of parathyroid hormone-related protein by the tumor.
  - Hypercalcemia is uncommon in Wilms tumor but is associated with congenital mesoblastic nephroma.
- Liver function test:
  - These may be abnormal in infants and children with metastases from a renal malignant rhabdoid tumor.
- No pathognomonic radiological features help distinguishing malignant rhabdoid tumor from the other renal tumors of childhood.
- There are however several features that may raise the suspicion for malignant rhabdoid tumor.
- Abdominal CT-scan and MRI (Figs. 4.82, 4.83, 4.84, 4.85, 4.86, and 4.87):

– Malignant rhabdoid tumor typically appears as a large, lobulated mass in the center or periphery of the kidney.

– The margins of the tumor may be sharply defined from the adjacent renal parenchyma, or they may be indistinct.

– Tumoral lobules are often separated by hypoattenuating areas of hemorrhage or necrosis.

– Calcification occurs frequently in malignant rhabdoid tumor.

– Malignant rhabdoid tumor–associated calcifications are often linear or curvilinear, and they may outline tumor lobules

– This is in contrast to Wilms tumor where calcification is seen in about 10 % only.

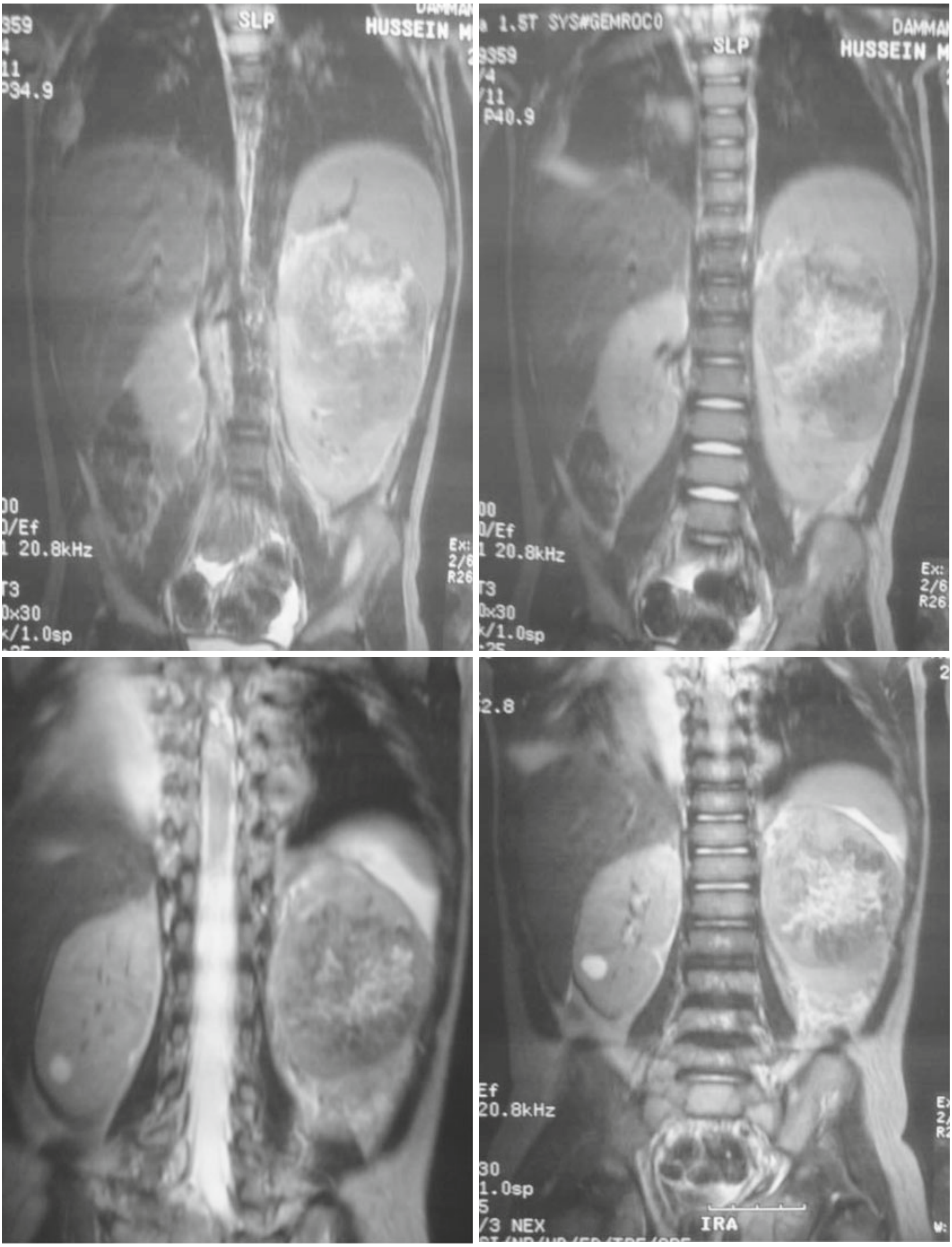
– Calcification is rarely seen in children with clear cell sarcoma or congenital mesoblastic nephroma.

– A peripheral, subcapsular, crescent-shaped fluid collection is often seen in association with malignant rhabdoid tumor.

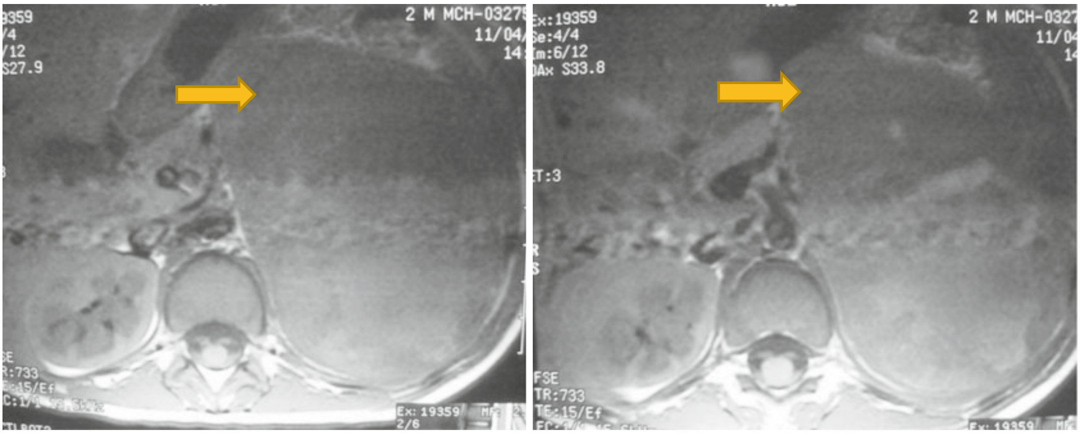
– These subcapsular fluid collections may be due either to hemorrhage or tumor necrosis.

– Subcapsular fluid collections are more common in patients with malignant rhabdoid tumor of the kidney than with the other renal neoplasms that occur in children.

– The relative frequency of subcapsular fluid collection in different pediatric renal tumors of the kidney is as follows:
  - Malignant rhabdoid tumor of the kidney (70 %)
  - Wilms tumor (9 %)


SLP
HUSSEIN M
P34.9
20.8kHz
0x30
/1.0sp
1.5T SYS#GEMROCO
DAMMA
P40.9
IRA
/3 NEX

Figs. 4.82, 4.83, 4.84, and 4.85 Abdominal MRI showing a left renal tumor. This was resected and found to be malignant rhabdoid tumor of the kidney. Note the mass in the center of the kidney



Figs. 4.86 and 4.87 Abdominal MRI showing a large left renal tumor. Note the peripheral, subcapsular, crescent-shaped fluid collection

  - Mesoblastic nephroma (14 %)
  - Clear cell sarcoma of the kidney (25 %)
- Chest CT-scan:
  - The lungs remain the most common site of metastases from malignant rhabdoid tumor of the kidney.
  - Lungs metastases are seen in 83 % of patients with metastatic malignant rhabdoid tumor at diagnosis.
  - The metastases is usually bilateral.
- Abdominal ultrasonography:
  - This is important to demonstrate invasion of the renal vein and/or the inferior vena cava in patients with malignant rhabdoid tumor.
- Radiological evaluation of the brain is indicated to exclude the possibility of a synchronous primary or metastatic brain tumor.
- Bone Scan:
  - Bone metastases are present in 5 % of infants and children with metastatic malignant rhabdoid tumor at diagnosis.
  - A bone scan is important to exclude bone metastases.
- Tissue biopsy is required to make a definitive diagnosis of malignant rhabdoid tumor.
- Bone marrow aspiration and biopsy are not routinely necessary because malignant rhabdoid tumor rarely metastasizes to the bone marrow.
- Lumbar puncture is not routinely indicated unless a CNS tumor is diagnosed.
- Rhabdoid tumors of the kidney appear as large, centrally located, heterogeneous soft-tissue masses, involving the renal hilum with indistinct margins.
- Rhabdoid tumors are large and heterogeneous, usually located centrally within the kidney.
- They are lobulated with individual lobules separated by intervening areas of decreased attenuation, relating to either previous hemorrhage or necrosis.
- The histologic diagnosis of malignant rhabdoid tumor depends on identification of characteristic rhabdoid cells:
  - These are large cells with eccentrically located nuclei and abundant, eosinophilic cytoplasm.
- Calcification is relatively common, seen in 20–50 % of cases and is typically linear and tends to outline tumor lobules.
- Subcapsular fluid accumulation is said to be a relatively characteristic feature, not often seen in other pediatric renal tumors.
- The INI1 gene (SMARCB1) on chromosome 22q functions as a classic tumor suppressor gene.
- Deletions or LOH of 22q in 49/51 was also found in rhabdoid tumors.
- There have been reported cases of a child having both atypical teratoid rhabdoid tumors in the brain as well as rhabdoid tumors of the

kidney. It has been hypothesized that a germline INI mutation may predispose a child to these tumors.
- All rhabdoid tumors share deletions in the long arm of chromosome 22, mapped to the INI1 gene, believed to be a tumor suppressor.
- The following features help differentiate Malignant rhabdoid tumor of the kidney from Wilms tumor:
  - Subcapsular fluid collections: a rare finding in other renal tumors.
  - Tumor lobules separated by hypoattenuating areas of necrosis or hemorrhage
  - Calcifications
    - More common than in Wilms tumors
    - Typically linear distribution outlining tumor lobules
  - Vascular and local invasion is more common

4.5.6 Treatment and Outcome

- The treatment of children with malignant rhabdoid tumor of the kidney is surgical resection followed by chemotherapy.
- The tumor should be removed en bloc to avoid tumoral spillage into the peritoneal cavity because this spillage increases the stage of the tumor. If the mass involves the upper pole of the kidney, the adrenal gland should be removed.
- Lymph nodes from the iliac, para-aortic, and celiac areas should be sampled, even if they do not appear abnormal.
- If the tumor is bilateral or unresectable, biopsy should be performed and preoperative chemotherapy is started to shrink the tumor and facilitate subsequent resection.
- Chemotherapy for malignant rhabdoid tumor of the kidney was historically based on therapy for a Wilms' tumor.
- This included vincristine, actinomycin, and doxorubicin with or without cyclophosphamide.
- With these agents, the estimated survival rate for patients with malignant rhabdoid tumor of the kidney was only 23 %.
- To try to improve survival, a new regimen of chemotherapy consisting of carboplatin-etoposide alternating with cyclophosphamide was used. This however did not improve outcomes.
- Recent reports have documented successful outcomes in patients with metastatic malignant rhabdoid tumor treated with ifosfamide-carboplatin-etoposide (ICE) or ifosfamide-etoposide (IE) alternating with vincristine-doxorubicin-cyclophosphamide (VDC).
- On the basis of these reports, cyclophosphamide-carboplatin-etoposide (CCE) alternating with VDC is the main treatment now.
- Radiation therapy is a cornerstone of treatment for CNS malignant rhabdoid tumor of the kidneys.
- High dose chemotherapy with stem cell rescue are used to treat non-CNS malignant rhabdoid tumor.
- The prognosis for patients with a rhabdoid tumor of the kidney is much worse than that of patients with other malignant renal tumors.
- In contrast to a Wilms' tumor, malignant rhabdoid tumor of the kidney is characterized by:
  - Early onset of local and distant metastases.
  - Resistance to chemotherapy.
  - Whereas the overall survival rate for Wilms' tumors exceeds 85 %, the survival rate for rhabdoid tumor of the kidney is only 20–25 %.
  - Gross hematuria is a presenting feature in approximately 60 % of patients with malignat rhabdoid tumor of the kidney. By contrast, only 20 % of patients with Wilms' tumor have gross hematuria.
  - Fever is a presenting symptom in 50 % of patients with a malignant rhabdoid tumor of the kidney, compared with 25 % of patients with a Wilms' tumor.
  - Hypertension is observed in up to 70 % of patients with malignant rhabdoid tumor of the kidney.
- Malignant rhabdoid tumor of the kidney is a rapidly progressive tumor, with most deaths

occurring within 12 months of presentation.

- The most common sites of metastasis at presentation are:
  - The lungs
  - Abdominal lymph nodes
  - Liver
  - Brain
  - Bone
- Malignant rhabdoid tumor of the kidneys has the worst prognosis of all malignant renal tumors.
- Infants and children with malignant rhabdoid tumors of the kidneys have aggressive disease, typically with distant tumor spread at diagnosis.
- Frequently, they die early, an 86 % mortality rate (within 1–2 years) and 90 % tumor relapse despite intense multi-drug chemotherapy.
- As many as 20 % of patients with a malignant rhabdoid tumor of the kidney have synchronous or metachronous CNS lesions, including both metastases and second primary cancers.
- Mutations or deletions of the *SMARCB1/INI1* gene play a role in the development of malignant rhabdoid tumor.

4.5.7 Mortality/Morbidity

- The overall survival rate for patients with malignant rhabdoid tumor enrolled in NWTS 1–5 was only 23.2 %.
- Most patients present with stage III or IV disease.
- Patients with germline mutations of *SMARCB1* likely manifest disease at an earlier age, with a high risk of progression and inferior prognosis.
- Malignant rhabdoid tumor is a rapidly progressive tumor, with most deaths occurring within 12 months of presentation.
- The most common sites of metastasis at presentation are the lungs, abdominal lymph nodes, liver, brain and bone.
- A young age at diagnosis is strongly associated with an adverse outcome.
- The 4-year event-free survival rates according to age at diagnosis were:
  - 8.8 % for patients aged 0–5 months
  - 17.2 % for patients aged 6–11 months
  - 28.6 % for patients aged 12–23 months
  - 41.1 % for patients aged 24 months or older
- High-stage (stage III/IV) disease is correlated with an adverse outcome.
- The survival of patients with malignant rhabdoid tumor in NWTS was as follows:
  - Stage I (33.3 %)
  - Stage II (46.9 %)
  - Stage III (21.8 %)
  - Stage IV (8.4 %)
  - Stage V (0 %)

4.6 Renal Cell Carcinoma in Children

4.6.1 Introduction

- Renal cell carcinoma (RCC) is also known as hypernephroma, Grawitz tumor, and renal adenocarcinoma.
- It originates in the lining of the proximal convoluted tubules.
- In 1883, Paul Grawitz was the first to describe the morphology of small, yellow renal tumors.
- In 1894, Otto Lubarsch, coined the term hypernephroid tumor, which was amended to hypernephroma by Felix Victor Birch-Hirschfeld.
- Foot and Humphreys introduced the term Renal Celled Carcinoma to emphasize its origin from the renal tubules.
- Fetter modified the term to the now widely accepted term Renal Cell Carcinoma.
- In 1959, Oberling et al. described convincing histological evidence that RCC arise from the epithelial cells of the renal convoluted tubules.
  - They found that the tumor cell cytoplasm contained numerous mitochondria and deposits of glycogen and fat.
  - They identified cytoplasmic membranes inserted perpendicularly onto basement membrane with occasional cells containing microvilli along the free borders.
- RCC is the most common renal tumor in adults, responsible for approximately 90–95 % of cases.

- Renal cell carcinoma represents 2 % of malignant tumors in adults and is the third most frequent tumor of the urinary tract after prostate and bladder tumors.
- Renal cell carcinoma usually occurs in the age range of 50–70 years.
- On the other hand, in pediatric ages, only 2–3 % of malignant renal tumors are proved to be RCC.
- Whereas the peak of incidence in Wilms' tumor occurs around 3 years of age, RCC presents between 9 and 15 years of age.
- Renal cell carcinomas are rare in children, and they show significant differences in their histology and pathogenesis when compared to those seen in adults.
- The incidence of RCC increases with age.
- The incidence of renal cell carcinoma is estimated in 0.1–0.3 % of all tumors and 1.8–6.3 % of all malignant renal tumors in childhood.
- Recent studies showed that the RCC corresponds to:
  - 1.4 % of renal tumors in patients under 4 years old
  - 15.2 % of renal tumors in patients between 5 and 9 years
  - 52.6 % of renal tumors in patients from 10 to 15 years old
- In the pediatric age group, RCC is seen in patients with Von Hippel-Lindau disease, which is associated with retinal and central nervous system hemangioblastomas, pheochromocytomas, and pancreatic neuroendocrine tumors.
- RCC is generally symptomatic at diagnosis, and most children with RCC present with more locally advanced disease.
- Generally, there is no sex predominance for RCC in children unlike in adults, in which the tumor predominates in males.
- The most common form of presentation of RCC in children is macroscopic hematuria and abdominal or flank pain.
- Other less frequent symptoms are palpable abdominal mass, anemia, and fever.
- RCC is diagnosed as a solid mass with US and CT. However, it is generally difficult to differentiate it from Wilms' tumor before surgery in children.
- Calcification or high-density areas on CT have been reported in 14–28 % of RCCs in children.
- So far, no treatment protocols have been defined for children with RCC.
- Surgery is the mainstay of treatment and results in cure when the tumor is localized and completely resected.
- The importance of radiotherapy and immunotherapy is not clear and different chemotherapy regimens showed only minimal benefits when tested in clinical trials.
- Tumor staging is the most important prognostic factor.
- The overall 5-year survival is approximately 60 % and patients with stage IV has the worst prognosis.
- Radical nephrectomy associated with regional lymphadenectomy is the best treatment for RCC in childhood.

4.6.2 Histopathology

- The gross and microscopic appearance of renal cell carcinomas is highly variable.
- Gross features:
  - A yellowish, multilobulated tumor in the renal cortex, which frequently contains areas of necrosis, hemorrhage and scarring.
  - The tumor compresses the surrounding parenchyma, producing a pseudocapsule.
  - Most translocation-RCC and papillary RCC are circumscribed, single lesions.
  - Multifocality in pediatric RCC is unusual and when present may suggest an underlying syndrome, such as tuberous sclerosis or von Hippel-Lindau disease.
  - Renal medullary carcinomas have a strikingly infiltrative growth pattern typically involving the medulla.
  - Neuroblastoma-associated oncocytic RCCs are often multifocal or bilateral.
- Microscopic Features:
  - There are four major histologic subtypes of renal cell cancer:
    - Clear cell (conventional RCC, 75 %)
    - Papillary (15 %)

    - Chromophobic (5 %)
    - Collecting duct (2 %)
- Sarcomatoid changes can be observed within any RCC subtype and are associated with more aggressive clinical course and worse prognosis.
- The tumor cells are quite large, atypical, and polygonal.
- They can be arranged in papillae, tubules or nests.
- The cells often contain large amounts of clear to variably eosinophilic cytoplasm and possess distinct cell borders separated by thin fibrovascular septa.
- The most common cell type exhibited by renal cell carcinoma is the clear cell, which is characterized by high lipid content in the cytoplasm.
- The clear cells are thought to be the least likely to spread and usually respond more favorably to treatment.
- Most of these tumors however, contain a mixture of cells.
- Small psammomatous calcifications are variably present.
- The majority have a Furman nuclear grade of 3, with easily identified nucleoli.
- Tumors containing the *ASPL-TFE3* phenotype tend to have abundant, voluminous cytoplasm that often contains cytoplasmic granules and eosinophilic bodies.
- Tumors with *PRCC-TFE3* gene fusion often have less abundant cytoplasm, are arranged more compactly, contain fewer calcifications, and display lower nuclear grades.
- Papillary RCCs:
  - Are composed of cells arranged in tubular and papillary configurations.
  - Often contain foamy macrophages.
  - Are typically encapsulated, although the tumor often penetrates its fibrous pseudocapsule.
  - Two types of papillary RCC are identified within the WHO classification.
    - Type 1 tumors are composed of cuboidal cells with little cytoplasm arranged in a single layer.
    - Type 2 tumors contain pseudostratified cells with higher nuclear grade and typically more eosinophilic cytoplasm.
- Renal Medullary Carcinomas:
  - These are usually composed of high-grade epithelial cells with acidophilic cytoplasm, arranged in a tubular, often cribriform architecture.
  - They occasionally are solid or sarcomatoid.
  - Characteristic microscopic features include desmoplasia and an acute inflammatory reaction.
  - The nuclei are large with prominent nucleoli in most cases.
  - The cells contain prominent eosinophilic cytoplasm with occasional rhabdoid-like cytoplasmic inclusion.
  - The nucleoli are often prominent.
- Post-neuroblastoma renal cell carcinomas:
  - These are single, bilateral, or multifocal tumors.
  - They are composed of solid and occasionally papillary cells with oncocytoid features and cellular heterogeneity.
  - Many cells contain copious eosinophilic cytoplasm with high nuclear grade, but others may lack these features.
- In 1982, Fuhrman recommended histologic grading for RCC.
- This is based on the microscopic morphology of a neoplasm with hematoxylin and eosin (H&E staining).
- This system categorizes renal cell carcinoma into four grades based on nuclear characteristics as follows:
  - Grade I:
    - Nuclei appear round and uniform, 10 μm; nucleoli are inconspicuous or absent.
  - Grade II:
    - Nuclei have an irregular appearance with signs of lobe formation, 15 μm; nucleoli are evident.
  - Grade III:
    - Nuclei appear very irregular, 20 μm; nucleoli are large and prominent.
  - Grade IV:
    - Nuclei appear bizarre and multilobated, 20 μm or more; nucleoli are prominent.
- Nuclear grade is believed to be one of the most imperative prognostic factors in patients with renal cell carcinoma.

4.6.3 Classification

- Pediatric renal cell carcinomas (RCC) account for approximately 2–3 % of all pediatric renal tumors.
- RCC arises from the cells of the proximal renal tubular epithelium.
- It is considered an adenocarcinoma.
- In 1826, Koenig published the first classification of renal tumors based on macroscopic morphology. He divided them into four forms:
  - Scirrhous
  - Steatomatous
  - Fungoid
  - Medullary
- There are two subtypes of renal cell carcinoma:
  - Sporadic
  - Hereditary
  - Both subtypes are associated with mutations in the short-arm of chromosome 3, with the implicated genes being either tumor suppressor genes (VHL and TSC) or oncogenes (like c-Met).
- RCCs is a heterogeneous group of tumors and have been classified into five subtypes based on the location within the nephron in which the tumors originate.
  - Clear-cell RCCs
  - Papillary RCCs
  - Chromophobe RCCs
  - Collecting duct carcinomas
  - Unclassified RCCs
- The most common subtypes of RCC seen preferentially in children are:
  - The translocation-associated renal cell carcinoma
  - Papillary renal cell carcinoma
  - Renal medullary carcinoma
  - Oncocytic renal cell carcinoma following neuroblastoma
- The histological diagnosis of renal cell carcinoma is made difficult by the considerable heterogeneity within and overlap between each of the above subtypes and by similarities to other pediatric renal neoplasms.
- Up to 25 % of pediatric RCC cannot be readily classified due to atypical features.
- Translocation-RCC may occur following chemotherapy for other diseases.
- Papillary RCC comprises approximately 30 % of the total.
- Papillary RCC in children may arise in the setting of pre-existing neoplasms, including Wilms tumor, metanephric adenoma, and metanephric adenofibroma.
- True clear cell RCC are extraordinarily rare in childhood.
- Conventional clear cell RCC comprises 6–20 % of the total.
- Renal medullary carcinoma is a highly aggressive tumor arising in patients with the sickle cell gene.
- Oncocytic RCC had been identified in patients previously diagnosed with neuroblastoma.
- Pediatric RCC differ in histologic appearance and genetic features from those seen in adults.
  - The most common are the Xp11 (TFE3) translocation-RCC (20–40 % of total).
  - TFE3 translocations involving a multitude of variant partners.
  - Translocations involving chromosome 17 [t(X;17)(p11.2;q25), ASPL-TFE3 fusion] and chromosome 1 [t(X;1)(p11.2;q21), PRCC-TFE3 fusion].
  - Contemporary investigation of pediatric RCC has demonstrated that a large percentage of these tumors bear cytogenetic translocations involving the MiT family of transcription factors.

4.6.4 Staging

- The staging of renal cell carcinoma is the most important factor in predicting its prognosis.
- There are several staging systems for renal cell carcinoma.
- Staging can follow the TNM staging system based on:
  - T: The size and extent of the tumor
  - N: Involvement of lymph nodes
  - M: Metastases
- It should be noted that tumor size, as measured in greatest dimension, is a critical fea-

ture of the TNM staging system most commonly utilized in the evaluation of RCC.

- Staging can also follow the stage grouping into stage I–IV.
  - Stage I: Tumor limited to kidney, <2.5 cm in diameter
  - Stage II: Tumor limited to kidney, >2.5 cm in diameter
  - Stage III: Tumor extends into renal vein, inferior vena cava, and perinephric tissue or adrenal glands but does not traverse Gerota fascia; nodal metastases <2 cm in diameter
  - Stage IV: Tumor extends beyond Gerota fascia or nodal metastases >2 cm in diameter margins and no capsule
- Staging of Renal Cell Carcinoma was also based on a different group staging into stage I–IV.
  - Stage I:
    - Tumor of a diameter of 7 cm (approx. 23⁄4 in.) or smaller, and limited to the kidney. No lymph node involvement or metastases to distant organs.
  - Stage II:
    - Tumor larger than 7.0 cm but still limited to the kidney. No lymph node involvement or metastases to distant organs.
  - Stage III:
    - Tumor of any size with involvement of a nearby lymph node but no metastases to distant organs.
    - Tumor of this stage may be with or without spread to fatty tissue around the kidney, with or without spread into the large veins leading from the kidney to the heart.
  - Stage IV:
    - Tumor with spread to fatty tissue around the kidney and/or spread into the large veins leading from the kidney to the heart, but without spread to any lymph nodes or other organs.
    - Tumor with spread to fatty tissue around the kidney and/or spread into the large veins leading from the kidney to the heart, but without spread to any lymph nodes or other organs.
    - Tumor that has spread directly through the fatty tissue and the fascia ligament-like tissue that surrounds the kidney.
    - Involvement of more than one lymph node near the kidney.
    - Involvement of any lymph node not near the kidney.
    - Distant metastases, such as in the lungs, bone, or brain.
- At diagnosis, 30 % of renal cell carcinomas have spread to the ipsilateral renal vein, and 5–10 % have continued into the inferior vena cava.

4.6.5 Clinical Features

- The clinical presentation include:
  - Hematuria (35–40 %)
  - Flank pain (40–50 %)
  - Abdominal mass (25–35 %)
  - Loss of appetite and weight loss (33 %)
  - Fever (20 %)
  - Hypertension (20 %)
  - Anemia
  - Night sweats
  - Malaise, fatigue and generally feeling unwell
  - Left varicocele in males
- The classic triad of RCC is seen in 10–15 % of patients and include:
  - Haematuria
  - Flank pain
  - Abdominal mass
- Children with RCC mostly present with more locally advanced disease.
- RCC commonly metastasize to the lymph nodes, lungs, liver, adrenal glands, brain or bones.
- Metastases occur in:
  - Lungs (40–65 %)
  - Liver (35–57 %)
  - Bones (10–42 %)
  - Bladder, brain or pleura (7–15 %)
- Renal cell carcinoma is one of the cancers most strongly associated with paraneoplastic syndromes (PNS), most often due to ectopic hormone production by the tumor.

- These are seen in about 20 % of patients and include:
  - Hypercalcemia
  - Polycythemia
  - Thrombocytosis
  - Secondary amyloidosis
- Several factors contribute to the outcome of RCC and these include:
  - Patient age
  - Tumor size
  - Histological pattern
  - Vascular invasion
- The overall survival rate of pediatric RCC is around 63 % and it is different according to the stage at diagnosis:
  - Stage I (92.4 %)
  - Stage II (84.6 %)
  - Stage III (72.7 %)
  - Stage IV (13.9 %)
- Most recurrences and deaths usually occur within the first 2 years after diagnosis, although late recurrences are frequent and long term follow up is important.
- Renal cell carcinoma is associated with von Hippel–Lindau syndrome, in which the tumors tend to be multiple and manifest at a younger age.
- This syndrome must be ruled out in pediatric patients diagnosed with renal cell carcinoma, especially when the tumor is bilateral.

4.6.6 Investigations

- Urine analysis
- Complete blood cell count
- Liver function testes
- Serum electrolytes, BUN and creatinine
- Pelvic and abdominal CT scans
- Ultrasound
- MRI scans
- Intravenous pyelogram (IVP) or renal angiography
- Radiologically, RCC is indistinguishable from Wilms tumor, though it tends to be smaller at presentation.
- The tumor invades locally with spread to adjacent retroperitoneal tissue.
- Imaging studies demonstrate a large solid intra-renal mass that typically involves the renal sinus.
- The mass replaces a large portion of renal parenchyma and may contain cystic, hemorrhagic, and necrotic regions.
- There is distortion of the normal renal architecture and formation of a pseudocapsule.
- There is a higher frequency of calcification in renal cell carcinoma (25 %) than in Wilms tumor (9 %).

4.6.7 Management

- The treatment depends on several including:
  - Stage of renal cell carcinoma
  - Organs and parts of the body affected/unaffected
  - Type of renal cell carcinoma
  - Pre-existing or comorbid conditions
  - Overall health and age of the person
- Radical nephrectomy (removing the entire affected kidney together with Gerota's fascia, the adrenal gland, and the regional lymph nodes) is the treatment of choice.
- The precise role of lymph node dissection is still controversial.
- Geller and Dome reported a 72.4 % disease free survival in patients with RCC and positive nodal disease. Among those with positive nodes who underwent adjuvant chemotherapy or radiotherapy, no improvement in disease-free or overall survival was noted. They concluded that lymphadenectomy in the absence of clinical or radiographic suspicion for nodal involvement confers no benefit.
- Prior to this, it is important to note that the other kidney must be fully functional.
- Nephron-sparing partial nephrectomy is used when the tumor is small.
- The presence of metastasis is not a contraindication to nephrectomy and if the metastasis is small this can also be surgically removed.
- Chemotherapy and radiotherapy are not as successful in treating RCC.
- Adjuvant chemotherapy has not been found to be beneficial in renal cell carcinoma.

- Neoadjuvant chemotherapy has been shown to decrease the size and stage of RCC and this allow it to be surgically removed. This may be useful in those with large non resectable tumors but the effectiveness of this approach is still being assessed.
- Immunotherapy with interferon or interleukin for the treatment of advanced RCC have been reported, but the benefits of these are uncertain in children.
- The role of new agents such as tyrosine kinase inhibitors is not well established in children with RCC.
- Metastatic renal cell carcinoma:
  - Metastatic renal cell carcinoma has a poor prognosis.
  - The tumor is extremely resistant to chemotherapy, rendering metastatic disease difficult to treat.
  - 25–30 % of patients with RCC have metastatic spread at the time of diagnosis.
  - The most common sites for metastasis are the lymph nodes, lung, bones, liver and brain.
  - The 5 year survival rate for metastatic renal cell carcinoma remains under 10 % and 20–25 % of these patients remain unresponsive to all treatments and the disease progress rapidly.
  - Interleukin-2 is considered a standard treatment for those with advanced renal cell carcinoma.
  - Other new treatments specifically designed for metastatic renal cell carcinoma include:
    - Sunitinib
    - Temsirolimus
    - Bevacizumab
    - Sorafenib
    - Everolimus
    - Pazopanib
    - Axitinib
  - These new treatments inhibit the growth of new blood vessels in the tumors, slow the growth and in some cases reduce the size of the tumors.
  - Side effects are common with these treatments and include:
    - Gastrointestinal side effects: Nausea, vomiting, diarrhea, anorexia
    - Respiratory side effects: Coughing, difficulty in breathing
    - Cardiovascular side effects: Hypertension
    - Neurological side effects: Intracranial hemorrhage, thrombosis in the brain
    - Skin and mucus membranes side effects: Rashes, hand-foot syndrome, stomatitis
    - Bone marrow suppression
    - Renal side effects: Impaired kidney function
    - Fatigue
  - Radiotherapy and chemotherapy are more commonly used to treat metastatic RCC.
  - These are not curative but are useful to relief symptoms related to the metastasis.

4.6.8 Prognosis

- The prognosis for renal cell carcinoma is largely influenced by a variety of factors, including:
  - Tumor size
  - Degree of invasion
  - Metastasis
  - Histologic type
  - Nuclear grade
- The prognosis is influenced most by the stage at presentation, with an overall survival rate of approximately 64 %.
- Renal cell carcinoma does not generally respond to chemotherapy or radiation.
- For those that have tumor recurrence after surgery, the prognosis is generally poor.

4.7 Angiomyolipoma of the Kidney

4.7.1 Introduction

- Angiomyolipomas are the most common benign tumor of the kidney.
- They are classically composed of blood vessels, smooth muscle cells and fat cells.
- It has an incidence of about 0.3–3 %.

- About 80 % of cases are sporadic and these are most commonly found in middle-aged women (mean age of presentation 43 years).
- There is a strong female predilection (F: M of 4:1) in sporadic angiomyolipomas.
- The remaining 20 % are seen in association with tuberous sclerosis, although they have also been described in Von Hippel-Lindau syndrome (VHL) and neurofibromatosis type 1 (NF1).
- In patients with tuberous sclerosis, 67–85 % will have renal angiomyolipoma by around 10 years of age.
- In these cases they present earlier (usually identified by the age of 10 years), are larger, fat-poor and are far more numerous.
- Angiomyolipomas are strongly associated with tuberous sclerosis.
- Patients with tuberous sclerosis tend to have several angiomyolipomas affecting both kidneys.
- Angiomyolipomas are also commonly found in women with the rare lung disease lymphangioleiomyomatosis.
- They can spontaneously hemorrhage, which can be fatal.
- The classic microscopic features of angiomyolipoma is myoid cells with clear cytoplasm spinning off of large vessels in a background of mature fat.
- Angiomyolipomas are caused by mutations in either the TSC1 or TSC2 genes, which govern cell growth and proliferation.
- Angiomyolipomas are usually benign but they may grow in size to an extent that the kidney function is impaired or leads to hemorrhage.

4.7.2 Histopathology

- Angiomyolipomas are members of the perivascular epithelioid cells tumour group (PEComas).
- They are composed of variable amounts of three components:
  - Blood vessels (-angio)
  - Plump spindle cells (-myo)
  - Adipose tissue (-lipo)
- Almost all classic angiomyolipomas are benign.
- They have the risk of rupture with bleeding or secondary damage/destruction of surrounding structures as they grow.
- There is a special variant called an epithelioid angiomyolipoma.
  - This is composed of more plump, epithelial looking cells, often with nuclear atypia.
  - These have a risk of malignant behavior.
  - They mimic renal cell carcinoma.
  - Metastases from this type have also been described.

4.7.3 Classification

- Angiomyolipomas are known as a PEComa, from the initials of perivascular epithelioid cell.
- They consist of perivascular epithelioid cells (cells which are found surrounding blood vessels and which resemble epithelial cells).
- In the past, these tumors were considered as hamartomas (benign tumors consisting of cells in their correct anatomical location but forming a disorganized mass).
- They were also considered as a choristoma (benign tumors consisting of normal cells but in the wrong location).
- Angiomyolipomas are considered as mesenchymal tumors composed of varying proportions of vascular cells, immature smooth muscle cells and fat cells.
- These three components respectively give rise to the components of the name: angio-, myo- and lip-. The -oma suffix indicates a tumor.
- Angiomyolipomas are typically found in the kidney but have also been found in the liver and less commonly the ovary, fallopian tube, spermatic cord, palate and colon.
- Angiomyolipomas occur in young women with lymphangiomyomatosis without other stigmata of tuberous sclerosis.
- Angiomyolipoma is also associated with neurofibromatosis and von Hippel–Lindau syndrome.
- In children, angiomyolipomas are rare in the absence of tuberous sclerosis.

- Eighty percent of children with tuberous sclerosis may be expected to develop angiomyolipomas by the age of 10 years.
- There are two types of angiomyolipoma:
  - Sporadic (isolated) angiomyolipoma
    - This accounts for 80 % of the cases.
    - Usually solitary.
    - The mean age at presentation is 43 years.
    - It is four times more common in women than in men.
    - 80 % of the cases involve the right kidney.
  - Angiomyolipoma associated with tuberous sclerosis
    - This accounts for 20 % of the cases.
    - The lesions are typically larger than isolated angiomyolipomas.
    - They are often bilateral and multiple
    - They occur equally in males and females
    - Angiomyolipomas occur in 80 % of patients with tuberous sclerosis.

4.7.4 Clinical Features

- Angiomyolipomas are often found incidentally when the kidneys are imaged for other reasons, or as part of screening in patients with tuberous sclerosis.
- Symptomatic presentation is most frequently with spontaneous retroperitoneal hemorrhage.
- The risk of bleeding being proportional to the size of the lesion (>4 cm diameter).
- Shock due to severe hemorrhage from rupture is described as Wunderlich syndrome.
- An angiomyolipoma larger than 5 cm and those containing an aneurysm pose a significant risk of potentially life-threatening rupture.
- Sometimes, the renal angiomyolipomas affect both kidneys to the extent that the renal function is impaired leading to chronic renal disease and renal failure.
- The retroperitoneal hemorrhage causes sudden pain, accompanied with nausea and vomiting.
- Up to 20 % of those with who present with retroperitoneal hemorrhage will be in shock.
- Patients may also present with numerous other symptoms and signs including:
  - A palpable mass
  - Flank pain
  - Urinary tract infections
  - Hematuria
  - Renal failure
  - Hypertension

4.7.5 Investigations

- CBC
- Electrolytes, BUN and creatinine
- PT and PTT
- Abdominal ultrasound:
  - This reveals hyperechoic lesions located in the renal cortex and with posterior acoustic shadowing.
  - In those with tuberous sclerosis, angiomyolipomas may be so numerous that the entire kidney is affected, appearing echogenic with loss of normal cortico-medullary differentiation.
- Abdominal CT-scan:
  - This reveals lesions involving the renal cortex and demonstrate macroscopic fat (less than -20 HU).
  - It is important to realize that a proportion of angiomyolipomas are fat-poor.
  - This is seen in those with tuberous sclerosis.
  - Calcification is rare in these tumors.
- Abdominal MRI:
  - MRI is excellent to diagnose angiomyolipomas because of their high fat content.
  - It can be difficult to distinguish a fat-poor angiomyolipoma from a renal cell carcinoma.
  - The presence of fat is not pathognomonic of angiomyolipomas and it is important to note that rarely renal cell carcinomas may have macroscopic fat components.
  - The absence of calcification on CT-scan or MRI favors the diagnosis of angiomyolipomas.
- Angiography:
  - Angiomyolipomas are hypervascular lesions demonstrating often characteristic features:

  - Micro- or macro-aneurysms
  - Sharply marginated
  - Dense early arterial network
  - Late whorled appearance
  - Absent AV shunting

4.7.6 Treatment and Prognosis

- Small angiomyolipomas found incidentally usually require no therapy.
- These should be followed-up to assess for growth.
- Very small solitary angiomyolipomas (<20 mm) do not require follow-up due to their slow growth.
- Large angiomyolipomas and symptomatic angiomyolipomas should be treated electively by:
  - Embolization
  - Partial nephrectomy
- Angiomyolipomas that present with retroperitoneal hemorrhage are treated with emergency embolization and nephrectomy should be avoided unless no interventional radiological facility is available.
- Angiomyolipomas smaller than 4 cm in diameter are typically asymptomatic; those larger than 4 cm in diameter are more likely to spontaneously hemorrhage, leading to flank or abdominal pain, hematuria, or even severe life-threatening hemorrhage.
- Severe retroperitoneal hemorrhage has been termed Wunderlich syndrome.
- Rarely, angiomyolipoma may become locally aggressive and invade neighboring structures. Extension into the inferior vena cava and regional lymph nodes has been described.
- The recent literature advocates US evaluation of patients with tuberous sclerosis every 2–3 years before puberty and yearly thereafter to identify growing lesions.
- Angiomyolipomas larger than 4 cm in diameter should be treated with partial nephrectomy or selective catheter embolization to prevent potentially life-threatening hemorrhage.
- In tuberous sclerosis, typically many angiomyolipomas affect each kidney and it is vital to preserve as much kidney tissue as possible when removing any lesion.
- Large angiomyolipomas are treated by embolization which reduces the risk of hemorrhage and can also shrink the lesion.
- A side effect of this treatment is postembolisation syndrome.
- Post-embolization syndrome usually lasts for few days and includes:
  - Severe abdominal pain
  - Fever
  - Nausea and vomiting

4.8 Renal Lymphoma

4.8.1 Introduction

- Primary Renal lymphomas (PRL) are defined as lymphomas arising in the renal parenchyma and not invasion from an adjacent lymphomatous mass or as a part of disseminated disease.
- In 1980, Coggins reported the first patient diagnosed with a PRL.
- Primary renal lymphoma is very rare.
- PRL accounts for 0.7 % of all extranodal lymphomas and represents less than 1 % of all renal tumors.
- Lymphomatous involvement of the kidney is often seen as a part of disseminated disease.
- PRL is a rare disease in which the etiology and pathogenesis are unclear.
- The kidneys are involved in 12 % of children with non-Hodgkin's lymphoma.

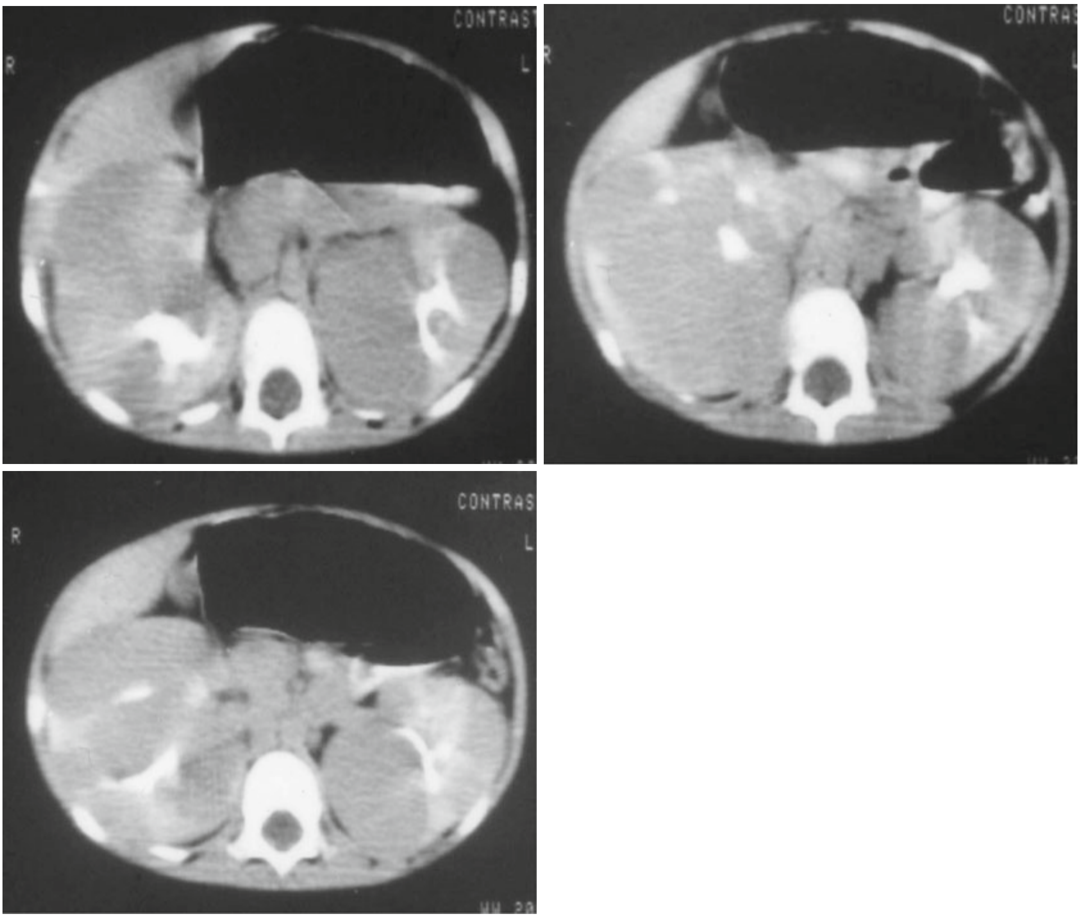
4.8.2 Etiology and Pathogenesis

- Primary lymphoma of the kidney is extremely rare since the kidney has no lymphatic system.
- Renal involvement is mainly due to hematogenous or direct spread of lymphoma from adjacent lymph nodes.
- The proposed pathogenetic mechanismsof renal lymphomas include:
  - Origin in the subcapsular lymphatics
  - Seeding via hematogenous route

  - Extension from retro peritoneal disease or inflammatory disease with a lymphoplasmacytic infiltrate

4.8.3 Diagnosis

- Lymphoma commonly involves the kidney secondarily from direct retroperitoneal extension or hematogenous metastases.
- As many as 62 % of patients with lymphoma have renal involvement at autopsy, although only 3 %–8 % of these patients demonstrate renal involvement on abdominal CT-scan (Figs. 4.88, 4.89, and 4.90).
- Primary renal lymphoma is very rare.
- Malbrain proposed several criteria to diagnose primary renal lymphoma as follows:
  - Acute renal failure at the presentation in the absence of other causes of renal impairment.
  - Rapid improvement of renal function after treatment
  - Increased kidney size without any urinary tract obstruction
  - Absence of other nodal involvement beyond the kidney
  - A confirmed diagnosis made by biopsy
- The most commonly encountered radiological feature is that of multiple soft tissue masses, ranging from 1 to 3 cm, with minimal enhancement after contrast compared to surrounding renal parenchyma.
- The presence of solitary renal lesion makes it difficult to diagnosis as it resembles the more common renal cell carcinoma (RCC).



Figs. 4.88, 4.89, and 4.90 Abdominal CT-scan showing bilateral renal lymphoma

- The differentiating features of renal lymphomas include:
  - Absence of calcification
  - Post contrast homogenous attenuation
  - Absence of renal vein thrombus
  - Absence of a mass effect on renal vessels and pelvicalyceal system in PRL.
  - However, this situation still demands a biopsy to rule out RCC.
- Other less commonly seen patterns in those with renal lymphomas include:
  - Enlarged non enhancing kidneys
  - Direct invasion of renal sinus and hilum by bulky retroperitoneal mass
  - A diffuse perirenal infiltration encasing the kidney
  - Most of the patients also have adjacent retroperitoneal adenopathy.
- MRI is currently becoming the imaging modality of choice for evaluation of renal lesions.
  - Lower signal intensity on unenhanced T1-weighted images than normal renal cortex and less enhancement on early gadolinium-enhanced images differentiates renal lymphoma from renal cell carcinoma.
- It is essential to differentiate between renal cell carcinoma and renal lymphoma in patients presenting with solitary renal masses.
- Preoperative biopsy is worthwhile in patients with atypical radiological features, since it may avoid nephrectomy.
- The most common histological subtype encountered is diffuse large B cell lymphoma (DLBCL).
- Lymphoma may also mimic nephroblastomatosis, however, lymphoma occurs typically in older children and is associated with lymphadenopathy elsewhere in the body.
- Imaging findings of renal lymphoma are variable and include:
  - Solitary or multiple renal masses or nodules
  - Diffuse infiltration
  - Direct invasion from contiguous retroperitoneal extension
  - Isolated perinephric disease
  - The most common radiologic pattern is multiple parenchymal masses or nodules that occasionally distort the renal contour and displace the collecting system.
  - They are usually homogeneous, are hypo attenuating on nonenhanced and contrast-enhanced images, and may mimic multiple renal cysts.
  - At US, they are hypoechoic
  - Angiography shows hypovascular mass lesions
  - Diffuse infiltration of the kidney may result in reniform enlargement.
  - Retroperitoneal disease occasionally leads to vascular and ureteral encasement.
  - Perinephric involvement can arise from retroperitoneal disease or transcapsular spread of parenchymal involvement.
  - The CT findings of perinephric disease are variable and include small curvilinear areas of high attenuation, soft-tissue attenuation nodules, thickening of the Gerota fascia, or a mass contiguous with retroperitoneal disease.

4.8.4 Clinical Features

- Lymphomas are malignant tumors that are caused by lymphoid cell proliferation.
- Involvement of the kidney by lymphoma is a common late manifestation of advanced nodal disease.
- Renal involvement in non-Hodgkin's lymphoma is usually seen as a part of disseminated disease.
- PRL is a rare and uncertain entity because renal parenchyma lacks lymphatic tissue.
- The term primary renal lymphoma is used when the disease is localized to the kidney without any sign of other organ involvement or in which renal involvement is the presenting manifestation.
- The reported incidence is as high as 47 % in autopsy series of lymphomas but clinically recognized in only up to 15 % of patients.
- In children, non-Hodgkin lymphoma especially Burkitt lymphoma is more likely to involve the kidney.

- Lymphomatous involvement of the kidney typically does not produce symptoms until late in the disease.
- Renal involvement is normally unilateral.
- Bilateral involvement is unusual.
- The clinical presentation is similar to the other renal malignancies.
- Flank or abdominal pain is the most frequent symptom.
- PRL can present with proteinuria or nephrotic syndrome and rapidly progress to renal failure, especially when both kidneys are affected.
- PRL has been associated with inflammatory and infectious chronic diseases, such as chronic pyelonephritis, Sjögren's syndrome, systemic erythematous lupus, or Epstein-Barr virus.
- The clinical presentations of renal lymphomas include:
  - Flank or abdominal pain
  - Hematuria
  - Abdominal mass
  - Fever
  - Weight loss
  - Acute renal failure
  - Hypertension is rare

4.8.5 Treatment and Prognosis

- The treatment of renal lymphoma depends on the primary histological subtype. The addition of Rituximab to the standard CHOP chemotherapy may improve the dismal outcome reported so far.
- Diffuse Large B Cell Lymphoma (DLBCL) is the most common histology.
- A follicular lymphoma, small lymphocytic lymphoma or MALToma is not unusual.
- Patients with atypical features of renal cell carcinoma should undergo a preoperative percutaneous renal biopsy.
- Nephrectomy can be avoided if a preoperative diagnosis is made.
- Systemic chemotherapy is currently the first treatment option for PRL.
- Treatment is mainly with chemotherapy; however careful nephrological monitoring is necessary during treatment since excretion of tumor metabolites may result in renal obstructive or uric acid nephropathy.
- The treatment of non-Hodgkin's Lymphoma (NHL) has been revolutionized with addition of Rituximab to the standard chemotherapy. This may overcome the poor outlook of this rare presentation of lymphoma.
- PRL has a poor prognosis with rapid dissemination and a 75 % mortality rate 1 year after diagnosis.
- However, early diagnosis combined with chemotherapy + rituximab could improve survival rates.

4.9 Ossifying Renal Tumor of Infancy

- Ossifying renal tumor of infancy is a very rare benign renal tumor.
- Ossifying renal tumor of infancy was first described by Chatten in 1980 as a variant of pediatric renal tumors.
- It is an extremely rare, benign renal tumor with classic clinical, radiological and histopathological features.
- The Patients age at presentation ranges from 6 days to 14 months.
- Boys are more commonly affected than girls.
- The left kidney is affected much more than the right (80 %).
- The upper pole calices are the commonest site involved.
- Etiology:
  - The etiology of this tumor has not yet been established.
  - The origin and natural history of the lesion are also uncertain.
  - Some investigators believe that the ossification is the result of the osteogenic potential of urothelial cells.
  - Others hypothesize that the spindle cells within the lesion resemble those seen in intralobar nephrogenic rests and that these lesions may lie within the pathologic spectrum of Wilms tumor.

- Gross features:
  - The tumor is believed to arise from urothelium and is attached to the renal medulla, specifically the papillary region of the renal pyramids.
  - From this location, it extends in a polypoid fashion into the collecting system.
  - It is seldom more than 2–3 cm in diameter.
- Microscopic features:
  - At microscopic analysis, the lesion consists of three basic components:
    - An osteoid core
    - Osteoblasts
    - Spindle cells
  - Mature osteoid elements tend to be more prominent in older patients.
- Clinical features:
  - Hematuria is the usual presenting symptom.
  - This is intermittent painless gross hematuria.
  - In infants with gross hematuria and a calcified noninvasive mass in the pelvi-calceal system, renal ossifying tumor should be considered in the differential diagnosis.
- Investigations:
  - MRI or CT scan offers a good diagnostic guide.
  - Abdominal ultrasound, CT-scan or MRI offers a good diagnostic guide.
  - On abdominal ultrasound, the mass is echogenic with shadowing, and hydronephrosis may be present.
  - Abdominal CT-scan shows a well-defined mass, often calcified, with poor enhancement.
  - At imaging, the renal outline is usually maintained; however, filling defects with partial obstruction of the collecting system are often seen.
  - Because of its location within the collecting system and its characteristic ossification, ossifying renal tumor of infancy may mimic a staghorn calculus, which would be exceedingly rare in the age group in which this lesion occurs.
- Treatment:
  - The treatment is surgical excision.
  - Open pyelostomy and tumor enucleation
  - Partial nephrectomy
- The biologic behavior of ossifying renal tumor of infancy appears to be benign, with no reported cases of malignant change or spread.
- Surgical excision is curative.

4.10 Metanephric Adenoma

4.10.1 Introduction

- Metanephric adenoma is also known as nephrogenic adenofibroma or embryonal adenoma.
- Metanephric adenoma has been described in the past under other names such as néphrome néphronogène, metanephroider Nierentumor and nephroblastomartiges Nierenadenom.
- The term metanephric adenoma was suggested by Brisigotti, Cozzutto et al. in 1992.
- It is a benign renal tumor that can occur at any age.
- It has been reported in patients as young as 15 months and as old as 83 years (Mean age at onset is around 40 years).
- It is more common in females.
- It is usually unilateral, and no bilateral cases have been reported.
- The presenting features include abdominal pain, hypertension, hematuria, a flank mass, hypercalcemia, and polycythemia.
- Polycythemia is more frequent in MA than in any other type of renal tumor.
- The tumor is more commonly calcified than any other renal neoplasm
- Grossly, MA tumors appear tan in color with multiple foci of hemorrhage.
- MA is composed of tightly packed uniform small epithelial cells with small regular nuclei, a high nuclei-to-cytoplasm ratio, and no mitotic figures.
- At histologic analysis, there is proliferation of spindle-shaped mesenchymal cells encasing nodules of embryonal epithelium. Numerous psammoma bodies may be seen.

- It is important to consider metanephric adenoma in the differential diagnosis of pediatric renal masses, since its benign nature allows local surgical resection with sparing of normal ipsilateral renal tissue.
- It is different from mesonephric adenoma.
- Surgery is curative.

4.10.2 Histopathology

- Gross features:
  - The mean size of the tumor is 5.5 cm with a range 0.3–15 cm.
  - The tumors can be located at upper pole, lower pole or mid-hilar region of the kidney.
  - These tumors are well circumscribed but unencapsulated.
  - On cut section, the tumor is tan pink, with possible cystic and hemorrhagic foci.
  - Calcifications are uncommon, and only occur in approximately 20 % of cases.
- Microscopic features:
  - Microscopically, metanephric adenoma can have an appearance similar to a nephroblastoma (Wilms tumours), or a papillary renal cell carcinoma.
  - They show a uniform architecture of closely packed acinar or tubular structures of mature and bland appearance with scanty interposed stroma.
  - The cells are small with dark staining nuclei and no nucleoli.
  - Blastema is absent and glomeruloid figures are a striking finding.
  - The lumen of the acini may contain otherwise epithelial infoldings or fibrillary material but it is quite often empty.
  - Mitoses are absent.
  - The tumor cells characteristically have round nuclear membrane, no nucleoli, and fine chromatin.
- Metanephric adenoma lacks the frequent gain of chromosomes 7 and 17 and losses of the Y chromosome that are seen in patients with papillary renal cell carcinomas.

4.10.3 Diagnosis

- Metanephric adenoma (MA) is a rare, benign tumor of the kidney.
- Metanephric neoplasms comprise a spectrum of kidney tumors containing renal epithelial or stromal cells or both.
- Although metanephric adenoma (MA) is a rare, benign neoplasm of epithelial cells, it is often difficult to distinguish this entity from other malignant neoplasms preoperatively.
- The differential diagnosis of renal MA includes papillary renal cell carcinoma and epithelial Wilms tumor.
- It is most important to distinguish MA from papillary renal cell carcinoma.
- Currently, neither ultrasound nor CT scans can reveal distinct features of MA.
- Ultrasound scans show a mass that is well defined and solid with both hyperechoic and hypoechoic regions.
- Doppler evaluation shows the lesion to be hypovascular.
- CT scans show a non-distinct mass with low attenuation on contrast studies, and small calcifications may be present. The lesion enhances less than normal renal parenchyma.
- Fine needle aspiration can be used as another less invasive method to diagnose MA, but it is not as accurate as nephrectomy.
- Add to this the fact that cytological diagnosis using fine needle aspiration can be difficult.
- Despite being a benign lesion, MA should be routinely resected in order to confirm the diagnosis and rule out papillary renal cell carcinoma.

4.10.4 Clinical Features

- Metanephric adenoma (MA) is a rare neoplasm, accounting for 0.2 % of adult renal epithelial neoplasms.
- Metanephric adenoma can occur at any age.
- It has been reported in patients as young as 15 months and as old as 83 years.

- The majority of cases occurs in patients 50–60 years of age and is seen predominantly in females by a 2:1 ratio.
- MA is a rare neoplasm that often presents as an asymptomatic renal mass.
- The clinical presentation include:
  - Abdominal pain
  - Abdominal mass
  - Hematuria
  - Dysuria
  - Fever
  - Hypertension
  - Hypercalcemia
  - Polycythemia
- Among renal tumors, MA has the highest incidence (12 %) of polycythemia.
- Several tumors can resemble MA including Wilms tumor, metastatic lung carcinoma, and metastatic papillary thyroid carcinoma; however, it is most difficult to distinguish MA from papillary renal cell carcinoma.

4.10.5 Treatment

- Metanephric adenomas are benign tumors and because of this some advocate no treatment is needed.
- Although MA is usually benign, there are a few reported cases of metastatic disease.
- Surgical resection is important in order to confirm the diagnosis and rule out papillary renal cell carcinoma.
- Surgery is curative and no other treatment is recommended.

4.11 Multilocular Cystic Renal Tumor

- In 1956, Boggs and Kimmelstiel first proposed the true neoplastic nature of these lesions, suggesting the term benign multilocular cystic nephroma.
- Joshi and Beckwith proposed a modification to the existing terminology.
  - Their modification emphasized a neoplastic rather than a developmental or hamartomatous origin.
  - They recommended that the term cystic nephroma be used to describe a multicystic tumor lacking blastemal or other embryonal elements.
  - They suggested that the term cystic partially differentiated nephroblastoma (CPDN) be used to denote a predominantly cystic lesion without nodular solid regions and in which the septa contain blastemal or other embryonal elements.
  - Furthermore, they proposed that both terms be used as subsets of the category term multilocular cystic renal tumor.
- Multilocular cystic renal tumor has a bimodal age and sex distribution and tends to occur in children (mostly boys) between 3 months and 4 years of age and in adults (mostly women) between 40 and 60 years of age.
- Multilocular cystic renal tumor are usually solitary, but bilateral tumors have been described.
- Multilocular cystic renal tumor most frequently manifests in children as a painless abdominal mass or less commonly as hematuria and urinary tract infection.
- The differential diagnosis of a pediatric multilocular renal mass includes cystic nephroma, cystic Wilms tumor or renal cell carcinoma, clear cell sarcoma, cystic variants of mesoblastic nephroma, and multicystic dysplastic kidney.
- Multilocular cystic renal tumor is a term that encompasses two histologically distinct but grossly indistinguishable renal tumors:
  - Cystic nephroma
  - Cystic partially differentiated nephroblastoma (CPDN)
- A cystic nephroma is a rare benign renal tumor that is also known as:
  - Multilocular cystic nephroma
  - Mixed epithelial stromal tumor (MEST)
  - Renal epithelial stromal tumor (REST)
- Cystic nephroma is a purely multiloculated cystic mass characterized by multiple septations composed entirely of differentiated tissues, without blastemal elements.
- CPDN is also a multiloculated cystic mass without nodular solid components, but its septa contain embryonal cells.

- Multilocular cystic renal tumors primarily affect boys during early childhood, with a substantial number of the lesions containing blastema (CPDN), and adult women, with lesions that more commonly lack septal blastema (cystic nephroma).
- As a rule, nephrectomy is curative and the clinical course is benign, but CPDN may recur locally.
- Cystic nephroma and CPDN cannot be distinguished radiologically.
- The differential diagnosis includes other pediatric cystic renal tumors:
  - Wilms tumor with cyst formation due to hemorrhage and necrosis
  - Cystic clear cell sarcoma
  - Cystic mesoblastic nephroma
  - Cystic renal cell carcinoma
  - Multicystic dysplastic kidney
  - Segmental multicystic dysplasia in a duplicated renal collecting system
- A cystic nephroma:
  - This is a benign cystic lesion of the kidney of unknown etiology.
  - The first cystic nephroma was described by Edmunds in 1892 but it was called “cystic adenoma of the kidney.”
  - Subsequently, it was called “multilocular cyst of the kidney”.
  - Cystic nephromas usually occur before age 2 and after age 40.
  - Cystic nephroma has not been described either in the antenatal or neonatal periods, which should help to differentiate it from other tumors such as cystic mesoblastic nephroma.
  - They are not commonly found in adolescents and young adults.
  - In children, cystic nephromas are more commonly found in boys and in adults, it is more commonly found in females.
  - Bilateral cases are exceedingly rare.
  - The most common presenting symptoms and signs are:
    - Flank mass
    - Flank or abdominal pain
    - Urinary tract infection
    - Hematuria
  - The histopathologic characteristics of cystic nephromas are striking.
    - The gross specimen shows a cluster of noncommunicating cysts of varying sizes.
    - The cysts size ranges from several millimeters to 4 cm in diameter.
    - The cysts are well circumscribed by a thick outer pseudocapsule that compresses the adjacent normal renal parenchyma.
    - The lesion is usually 5–10 cm in diameter and may extend beyond the normal reniform configuration into the renal pelvis and the perinephric spaces.
    - The cysts are lined with flattened, cuboidal, or hobnail-appearing cells and to contain straw-yellow, proteinaceous, colloid-like fluid.
    - The intervening septations conform to the cyst contours and do not form nodular masses.
  - In a review of the literature, Joshi and Beckwith outlined the revised criteria for the diagnosis of cystic nephroma:
    - The lesion is composed entirely of cysts and their septa.
    - The lesion forms a discrete mass, well demarcated from the noncystic renal parenchyma.
    - The septa are the only solid portions of the tumor, conforming to the outlines without solid expansile nodules.
    - The cysts are lined by flattened, cuboidal, or hobnail-appearing epithelium.
    - The septa are composed of fibrous tissue in which well-differentiated tubules may be present but poorly differentiated tissues and blastemic cells are absent.
  - It is generally believed that well-differentiated, mature renal tubules and mature heterologous tissues, such as skeletal muscle and cartilage, may be found in cystic nephromas but that hemorrhage and necrosis are not observed.
  - There is controversy as to whether calcification may be found in cystic nephromas.

  - Radiologically, abdominal ultrasound, MRI and CT-scan are useful but a definitive diagnosis and exclusion of an associated malignancy cannot be ensured. This is even in spite of the addition of percutaneous biopsies.
  - The presence of solid components should discourage a diagnosis of cystic nephroma.
  - The treatment of choice for cystic nephroma is surgical extirpation.
  - Nephron-sparing surgery should be considered also.
  - Cystic nephromas are benign, and the possibility of a recurrence developing after complete surgical extirpation of the neoplasm is unlikely.
- Multilocular cystic renal tumor encompasses a spectrum ranging from a purely cystic lesion lined by epithelium and fibrous septa with mature tubules (cystic nephroma) to a lesion in which the septa contain foci of blastemal cells (cystic partially differentiated nephroblastoma).
- Cystic partially differentiated nephroblastoma is distinguished from cystic Wilms tumor by the absence of expansile solid masses of nephroblastomatous tissue.
- Cystic nephroma and cystic partially differentiated nephroblastoma are uncommon, benign lesions that cannot be differentiated by means of their gross or radiographic appearance.
- Multilocular cystic renal tumors tend to manifest at two age peaks:
  - In children aged 3 months to 4 years (predominantly boys with cystic partially differentiated nephroblastoma)
  - In adults (pre-dominantly women with cystic nephroma)
- Patients frequently present with a painless abdominal mass, and systemic symptoms are rare. Rarely, they present with hematuria or urinary tract infection.
- Abdominal ultrasound and CT-scan findings in those with multilocular cystic renal tumor (MCRT) include:
  - Large multilocular renal cystic mass sometimes extending into the renal hilum.
  - A well-circumscribed, encapsulated multicystic mass with variably enhancing septa and no excretion of contrast agent into the loculi.
  - The septae are of uniform thickness and only minimally hyperemic on color Doppler ultrasound.
  - The contents of the cyst may have similar or slightly higher attenuation than that of water, and if the cystic spaces are very small, the closely packed septa can mimic a solid mass.
  - On CT images, visualizing the symmetric excretion of contrast material by the remaining functioning renal parenchyma helps to differentiate MCRT from multicystic dysplastic kidney. However, it may be difficult to differentiate segmental multicystic dysplastic kidney from cystic nephroma on the basis of imaging alone.
- Cystic nephroma and CPDN are indistinguishable from one another based on their gross and radiographic appearances.
- Gross features:
  - MCRT is a well-circumscribed mass with a thick fibrous capsule that contains multiple, fluid-filled, noncommunicating loculi separated by thin translucent septa.
  - The loculi can range in size from microscopic to 4 cm in diameter.
- Microscopic features:
  - At microscopic examination, the septa are lined by flattened or cuboidal epithelia, with areas of eosinophilic cuboidal cells protruding into the lumen that produce a hobnail or teardrop appearance.
  - Mature renal tubules may be seen within the septa.
  - Unlike CPDN, cystic nephroma does not contain blastemal cells within the septa.
- Imaging studies demonstrate a well-circumscribed, encapsulated mass consisting of multiple cysts from several millimeters to 4 cm in diameter, with variably enhancing septa and no excretion of contrast material into the loculi.

- When the cystic spaces are small, the tumor may appear solid.
- Calcification, although uncommon, can be present and is defined as curvilinear and peripheral localizations.
- Because neither the clinical nor the imaging features of MCRT can predict its histologic characteristics, surgery either nephrectomy or nephron-sparing surgery is required for both diagnosis and treatment.
- If pathologic analysis proves that the tumor is a CPDN, regular noninvasive monitoring is suggested because the presence of blastemal cells in the septa of a CPDN implies the potential for more aggressive behavior, despite the usually benign course of the tumor.
- Treatment of these tumors is surgical excision, and the prognosis is excellent with complete excision.
- The rare cases in which there is tumor recurrence are successfully treated with local radiation therapy or chemotherapy.
- Metastatic disease has not been documented.

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Multi Cystic Dysplastic Kidney (MCDK)

5

5.1 Introduction

- Multicystic dysplastic kidney (MCDK), a variant of renal dysplasia results from the malformation of the kidney during fetal development.
- Other terms used to describe this condition include multicystic kidney and multicystic renal dysplasia.
- Renal dysplasia results from an abnormal metanephric differentiation.
- Renal dysplasia is the leading cause of end-stage renal disease in children.
- It consists of a spectrum of renal conditions, including:
  - Renal hypoplasia
  - Multicystic dysplastic kidney
  - Renal aplasia
- Multicystic dysplastic kidney is characterized by the presence of multiple, noncommunicating cysts of varying size separated by dysplastic parenchyma and the absence of a normal pelvicaliceal system (Fig. 5.1).
- The condition is associated with ureteral or ureteropelvic atresia, and the affected kidney is nonfunctional.
- Multicystic dysplastic kidney is the most common cause of an abdominal mass in the newborn period and is the most common cystic malformation of the kidney in infancy.
- Multicystic dysplastic kidney can be unilateral or bilateral.
- Those with bilateral disease often have other severe malformation syndromes.
- In bilateral cases, the newborn has the classic characteristic of Potter's syndrome.
- Bilateral multicystic dysplastic kidney is incompatible with survival.
- In those with unilateral multicystic dysplastic kidney:
  - Contralateral ureteropelvic junction obstruction is found in 3–12 % of infants.
  - Contralateral vesicoureteral reflux is seen in 18–43 % of infants.
  - A voiding cystourethrography should be part of the work up of these patients.
- The incidence of unilateral multicystic dysplastic kidney is reported to be 1 in 4,300 live births.
- The combined incidence of unilateral and bilateral multicystic dysplastic kidney is 1 in 3,600 live births.
- Bilateral multicystic dysplastic kidney occurs in about 20 % of prenatally diagnosed cases of multicystic dysplastic kidney.
- Unilateral multicystic dysplastic kidney is more common in males with a male-to-female ratio of 1.48:1.
- The left kidney is involved in 55 % of cases, and the right kidney is involved in 45 %.
- Diagnosed multicystic dysplastic kidney and on follow-up:
  - May persist without any change
  - May increase in size
  - May undergo spontaneous involution

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A.H. Al-Salem, *An Illustrated Guide to Pediatric Urology*, DOI 10.1007/978-3-319-44182-5_5

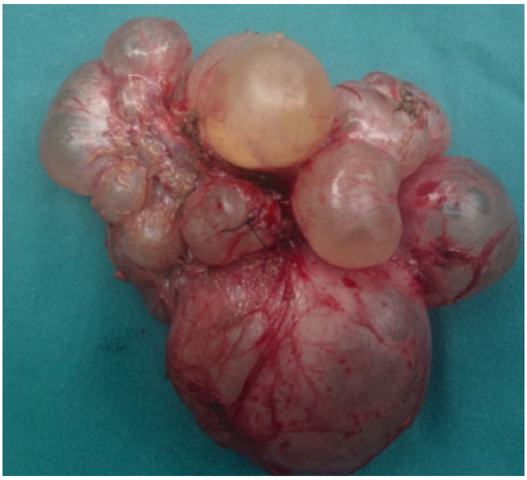


Fig. 5.1 A clinical photograph showing multicystic dysplastic kidney showing multiple noncommunicating cysts of varying sizes. These cysts are separated by dysplastic renal parenchyma and absence of pelvicaliceal system

- Most cases of unilateral multicystic dysplastic kidney undergo spontaneous involution.
- Calcification may develop in persistent multicystic dysplastic kidney.
- Multicystic dysplastic kidney is usually asymptomatic but can be complicated by:
  - Urinary tract infection (UTI)
  - Hypertension
  - Neoplasia

5.2 Embryology

- The urogenital system is predominantly derived from the intermediate mesoderm of the embryo.
- This intermediate mesoderm undergoes epithelial transformation to form the nephric duct.
- The nephric duct extends adjacent to another tract called the nephrogenic cord which is also derived from mesoderm.
- The nephric duct induces the adjacent nephrogenic cord mesenchyme to aggregate and transform into epithelial tubules.
- During its caudal migration, the nephric duct induces three embryonic kidneys in the nephrogenic cord:
  - The pronephros
  - The mesonephros
  - The metanephros
- Normal renal development is dependent upon the interaction of the metanephric bud and the metanephric blastema.
- The nephric duct gives rise to a caudal diverticulum called the ureteric bud.
- This invades the metanephric mesenchyme which becomes the ultimate kidney.
- The interactions between the metanephric mesenchyme and the ureteric bud leads to the development of the future kidney.
- This interaction results in the formation of calyces, tubules and nephrons.
- Complete obstruction or atresia impairs ureteral branching and results in decreased division of collecting tubules and inhibition of induction and maturation of nephrons.
- The collecting tubules enlarge and develop cysts in their terminal portions.
- These cysts of various sizes are distributed randomly throughout the abnormal kidney and are held together by connective tissue, without macroscopic evidence of intercommunication of cysts.
- In muticystic renal dysplasia the renal pelvis and or ureter are usually atretic.
- In this and other forms of dysplasia, the more proximal the level of obstruction, the more likely the cysts will be large.
- It has been hypothesized by Pathak et al. that these changes are the result of the pressure effects on the kidney from the obstruction.
  - Proximal obstruction results in calyces that are markedly distended with cyst formation.
  - In those with distal obstruction as in posterior urethral valves, the pressure effects are more generalized and less severe, so that the calyces do not distend as much. The kidneys will become dysplastic with much smaller and less visible cysts.

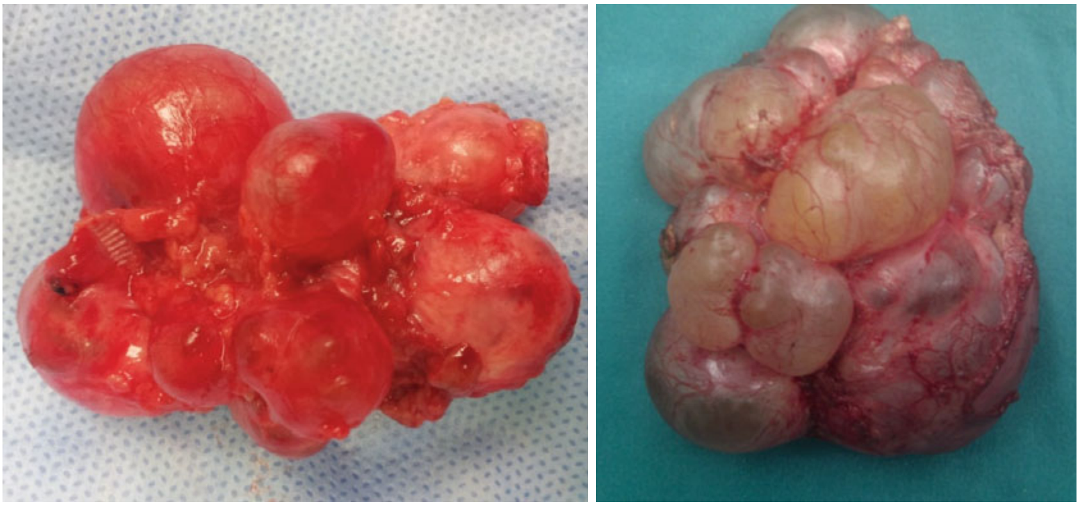
- During embryonic development the central elements of the kidney form first and the more peripheral elements form later.
- The metanephric mesenchyme forms the proximal components of the nephron from the glomerulus to the distal convoluted tubule.
- The ureteric bud that invades and branches inside the mesenchyme forms the distal components of the nephron, including the collecting ducts, calyces, pelvis, and ureter.
- The ureteric bud theory:
  - This was proposed by Mackie and Stephens
  - Multicystic dysplastic kidney results from an abnormal induction of the metanephric mesenchyme by the ureteral bud.
  - This abnormal induction might be due to:
    - A defect in the formation of the mesonephric duct
    - Malformation of the ureteric bud
    - Degeneration of the ureteric bud at an early stage.
  - The final shape of the dysplastic kidney depends on the timing of the defect to the ureteric bud and on the effect of this on the ureteric bud branching.
- Multicystic dysplastic kidney usually develops as a sporadic problem; although, familial cases have been reported.
- Mutations in genes important in ureteric bud development have been identified in syndromes with renal dysplasia, including multicystic dysplastic kidney. These include:
  - Mutations in *EYA1* or *SIX1* genes that lead to branchio-oto-renal (BOR) syndrome.
  - Mutations in the *PAX2* gene, the cause of Renal-coloboma syndrome (RCS), are associated with renal dysplasia.
  - Hereditary MCDK was found in three generations of a family that also carried a *PAX2* gene mutation.
  - *PAX2* mutations have also been identified in patients with isolated renal hypoplasia/dysplasia.
- Exposure to viral infections in utero has been associated with multicystic dysplastic kidney. These include cytomegalovirus (CMV), enterovirus, and adenovirus.
- Teratogens may also play a role in abnormal renal development. Although, their association with multicystic dysplastic kidney has not been clearly established.

5.3 Etiology and Pathophysiology

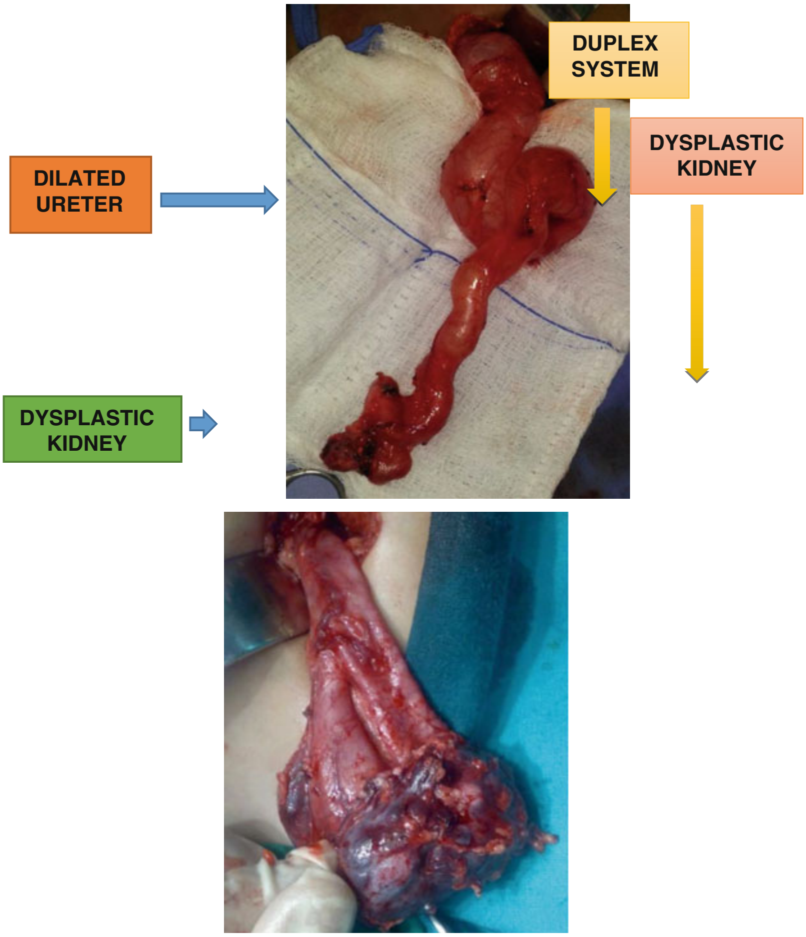
- The exact etiology of multicystic dysplastic kidney is not known.
- Genetic factors are important etiological factors for multicystic dysplastic kidney.
- Multicystic dysplastic kidney result from an abnormal induction of metanephric mesenchyme.
  - Some mutations in genes associated with renal dysplasia (in syndromes) have been determined.
  - These mutations occur at EYA1 or SIX1 genes (branchio-oto-renal syndrome).
  - The PAX2 gene is also thought to play a role in the etiology of multicystic dysplastic kidney.
- Multicystic dysplastic kidney can be a consequence of a genetic syndrome, which in turn may affect the digestive tract, nervous system, or other areas of the urinary tract.
- Medications such as antihypertensives taken by the mother during pregnancy may play a role in the pathogenesis of multicystic dysplastic kidney.

5.4 Histologic Findings

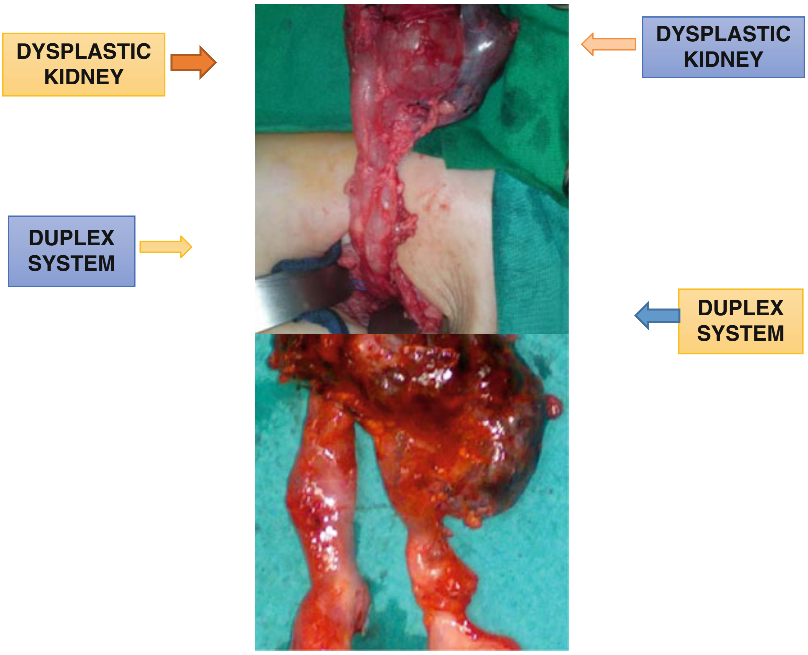
- Gross findings (Figs. 5.2, 5.3, 5.4, 5.3, 5.6, and 5.7):
  - The multicystic dysplastic kidney is enlarged, abnormally shaped, and often resembles a bunch of grapes (Figs. 5.2 and 5.3).
  - The kidney is composed of numerous and irregularly sized cysts.
  - The cysts range in size from less than 1 mm to several centimeters in diameter.
  - The number of cysts is also variable ranging from <5 cysts in 34 % of patients to >5 cysts in 66 % of patients.



Figs. 5.2 and 5.3 Clinical photographs showing multicystic dysplastic kidney. Note the kidney which is composed of multiple noncommunicating cyst of varying sized that resembles a bunch of grapes

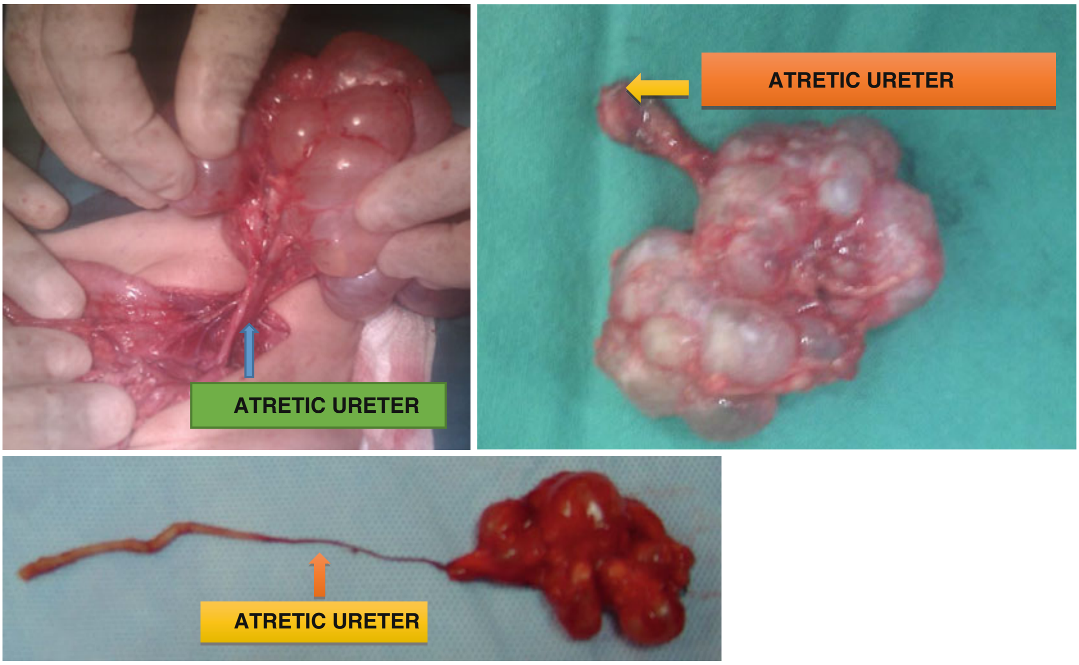

DUPLEX SYSTEM
DYSPLASTIC KIDNEY
DILATED URETER
DYSPLASTIC KIDNEY

Figs. 5.4 and 5.5 Intraoperative photographs showing small, dysplastic involuted kidneys. Note the duplex system on the right side



Figs. 5.6 and 5.7 Clinical photographs showing dysplastic kidneys in kidneys with duplex systems

- The cysts contain a clear or yellow fluid and are connected by a fibrous tissue stroma.
- Cysts may be quite large, as in the classic description of multicystic dysplastic kidney, or the kidney may be echogenic and dysplastic or small and involuted.
- It has been suggested that some cases of renal agenesis may be due to involuted cases of multicystic kidney disease.
- There is loss of kidney and pelvocaliceal differentiation.
- Rudimentary renal tissue or lobes are sometimes grossly identifiable.
- Sometimes, multicystic dysplastic kidney might be seen in only the upper or lower pole of a duplicated collecting system.
- Ureteral or ureteropelvic atresia is always present (Figs. 5.8, 5.9, and 5.10).
- The atretic portion of the ureter varies in length from 1 to 5 cm.
- The ipsilateral renal artery is absent or hypoplastic.
- The change in size of the cysts in multicystic renal dysplasia are likely related to the number of preserved glomeruli and thus the degree of residual renal function (Fig. 5.11).
- As long as the kidney is able to filter plasma, the overall size of the multicystic dysplastic kidney will increase.
- As the nephrons become fibrotic, the amount of filtrate will diminish and the growth of the kidney will stop and subsequently decrease in size.
- On follow-ups of multicystic dysplastic kidneys, it was shown that:
  - 70 % decrease in size
  - 20 % showed no change in size
  - 10 % increased in size
  - Microscopic findings:
- Histopathologic examination reveals abnormal ductal differentiation and only rudimentary corticomedullary differentiation.
- Thick-walled or thin-walled cysts with smooth inner linings are present throughout the kidney.



Figs. 5.8, 5.9, and 5.10 Clinical photographs showing multicystic dysplastic kidneys. Note the atretic ureters

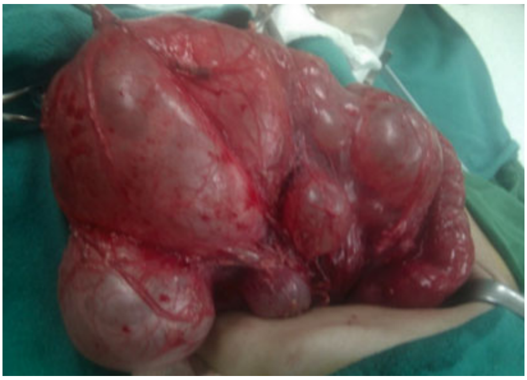


Fig. 5.11 Clinical intraoperative photograph showing multicystic dysplastic kidney showing multiple cysts of different sizes

- Normal renal parenchyma is usually absent.
- The loose connective tissue that surrounds the cysts might range from thin strands to extensive areas of fibrosis.
- Primitive epithelial ducts and nests of metaplastic cartilage are seen. These represent the principal microscopic criteria for a diagnosis of multicystic dysplastic kidney.
- Although the kidney in multicystic dysplasia is usually described as having no renal function, there is evidence that these kidneys may have some component of residual renal function.
- Microscopic examination of the MCDK has shown that the number of nephrons are reduced but are seldom absent.
- The glomeruli are primitive, and sometimes normal glomeruli may be seen.

5.5 The Natural History of Multicystic Dysplastic Kidney

- Multicystic dysplastic kidney can be diagnosed prenatally.
- Some cases of prenatally diagnosed multicystic dysplastic kidney monitored prior to birth

demonstrate an initial increase in size followed by involution.

- An involution of prenatally diagnosed multicystic dysplastic kidney has been noted before birth.
- The natural history of multicystic dysplastic kidney is variable:
  - They may persist without any change
  - They may increase in size
  - They may undergo spontaneous involution
  - Most cases of unilateral multicystic dysplastic kidney undergo spontaneous involution
- Calcification may develop in persistent multicystic dysplastic kidney.
- The Multicystic Kidney Registry reported 260 patients with multicystic dysplastic kidney whose cases were managed nonoperatively and whose cases were followed for varying periods as long as 5 years.
  - Approximately 18 % of these kidneys were undetectable by age 1 year.
  - 31 % were undetectable by age 3 years
  - 54 % were undetectable by age 5 years.

5.6 Classification

- Multicystic dysplastic kidney (MCDK) was first described as a distinct clinical entity by Spence in 1955.
- In 1986, the Urology Section of the American Academy of Pediatrics established the National Multicystic Kidney Registry, which is a large, multicenter, longitudinal database that has helped clarify the appropriate management of MCDK.
- Multicystic dysplastic kidney (MCDK) is a congenital maldevelopment of the kidney in which the renal cortex is replaced by numerous cysts of multiple sizes.
- A dysplastic parenchyma anchors the cysts, the arrangement of which resembles a bunch of grapes.
- No functional renal tissue can be identified.
- The calyceal drainage system of the affected kidney is absent.
- Typically, MCDK is a unilateral disorder and bilateral MCDK is incompatible with life.
- Several forms of MCDK have been described.
  - The classic type
  - The less common hydronephrotic type
  - A third type known as solid cystic dysplasia
- The classic type has a random configuration of cysts, whereas the hydronephrotic type presents with a discernible, dilated renal pelvis surrounded by cysts.
- The solid cystic dysplasia is composed of smaller cysts with a greater amount of nonfunctional parenchyma.
- MCDK should not be confused with polycystic kidney disease (PCKD) or other renal cystic diseases.
- The multicystic kidney is a dysplastic kidney which has been classified by Potter et al. as type II disease.
- Subsequently, this type has been sub classified into two groups:
  - Type IIa
  - Type IIb
  - The more common type IIa is secondary to pelvoinfundibular atresia.
  - Type IIb is the hydronephrotic form.
  - The pelvoinfundibular atresia and resulting dysplasia of MCKD is thought to result from a vascular insult.
  - MCKD have been reported to be familial in few cases.
  - Ipsilateral multicystic dysplastic kidney was also reported in identical twins.

Potter classification of renal dysplasia	
Type I	Autosomal recessive polycystic kidney disease (ARPKD)
Type IIa	Multicystic dysplastic kidney disease [pelvo-infundibular atresia] (MDKD)
Type IIb	Multicystic dysplastic kidney disease [hydronephrotic type] (MDKD)
Type III	Autosomal dominant polycystic kidney disease (ADPKD)
Type IV	Cystic dysplasia due to urethral obstruction

5.7 Associated Anomalies

- Multicystic dyplastic kidney is associated with contralateral renal disease in a significant number of patients.
- Previous reports have shown that MCDK is associated with a 20–45 % incidence of contralateral renal anomalies.
- The most common contralateral abnormality was vesicoureteral reflux and ureteropelvic junction obstruction.
- Bilateral MCDK was reported in 19 % and contralateral renal agenesis in 11 %.
- Contralateral hydronephrosis was seen in 7 %.
- 30–35 % of fetuses with MCDK have associated non-renal abnormalities.
- The most common abnormalities were those of the heart, followed by the spine, extremities, face and umbilical cord.
- Fetuses with bilateral MCDK are more likely to have associated non-renal abnormalities (66.7 %) in comparison with fetuses with unilateral MCDK (25.6 %).
- Abnormal chromosomes:
  - Abnormal chromosomes (10 %).
  - Female fetuses (20 %) are more likely to have an abnormal chromosome study than male fetuses (5.6 %).
  - Fetuses with bilateral MCDK disease (16.7 %) are more likely to have an abnormal karyotype than fetuses with unilateral MCDK (7.7 %).
  - No karyotype abnormalities were found in fetuses with unilateral MCDK if an associated non-renal abnormality was not found.
- The ratio of male to female fetuses was 2.4:1.
- Female fetuses were twice as likely to have bilateral MCDK as males.
- Vesicoureteic reflux in the contralateral kidney (23 %).
- As most patients with multicystic dysplastic kidneys have pelvo-ureteral atresia on the affected side, it is unlikely that infected urine will reflux into the kidney.
- Multicystic dysplastic kidney has been reported in various syndromes, including the following:
  - 49,XXXXX syndrome (hypertelorism, epicanthic folds, microcephaly, short neck, clinodactyly of the fifth finger, small hands and feet, and mental retardation).
  - Alagille syndrome (liver disease, cardiac defects, characteristic facies, renal anomalies, vascular anomalies and anomalies of the eye, pancreas, and skeletal system. The condition is associated with mutations in the *JAG1* gene that encodes for a ligand of Notch.
  - Beckwith-Wiedemann syndrome (macrosomia, microcephaly, macroglossia, visceromegaly, omphalocele, and hypoglycemia).
  - Branchio-oto-renal (BOR) syndrome (hearing loss, ear malformations, branchial cleft fistulas or cysts, and renal dysplasia or renal agenesis. The BOR syndrome is an autosomal dominant condition caused by mutations in the *EYA1* and *SIX1* genes.
  - Hypoparathyroidism-deafness-renal syndrome (sensorineural deafness, hypoparathyroidism, and urinary tract anomalies, including renal dysplasia). This autosomal dominant syndrome is caused by mutations in the *GATA3* transcription factor.
  - Joubert syndrome (hypoplasia of the cerebellar vermis, hypotonia, and impaired psychomotor development together with abnormal respiratory pattern, abnormal eye movements with poor vision, or both). This syndrome is an autosomal recessive condition.
  - Maturity-onset diabetes of the young type V (MODY5): MODY5 is a monogenic form of diabetes with an autosomal dominant mode of inheritance caused by mutations in the hepatocyte nuclear factor 1-beta mutations. Patients present with diabetes, usually when younger than 25 years, with a wide spectrum of renal anomalies, including cystic dysplasia.
  - Renal coloboma syndrome (RCS): The RCS is an autosomal dominant condition caused by mutations in the transcription factor *PAX2* and characterized by optic

  nerve coloboma and renal malformations, including dysplasia.
  - Trisomy 18: Patients with trisomy 18 have a prominent occiput, micrognathia, low-set ears, and flexion deformities of the fingers, congenital heart disease, and mental retardation.
  - VACTERL association: The VACTERL association refers to the combination of vertebral defects (V), anal atresia (A), cardiovascular anomalies (C), tracheoesophageal fistula (TE), renal anomalies (R), and limb defects (L). In 20 % of these patients, cystic renal disease may be found.
  - Waardenburg syndrome type 1: Patients present with developmental anomalies of the eyelids, eyebrows, and nose root; pigmentary defects of the iris and hair; and congenital deafness.
  - Williams' syndrome: This syndrome is characterized by elfin facies, mental retardation, supravalvular aortic stenosis, and neonatal hypercalcemia.
- Nonrenal malformations reported in patients with multicystic dysplastic kidney include the following:
  - Gastrointestinal malformations:
    - Duodenal atresia
    - Esophageal atresia
    - Hirschsprung's disease
    - Anorectal malformations
    - Inguinal hernia
    - Omphalocele
    - Tracheoesophageal fistula
  - Neurologic malformations
    - Anencephaly
    - Caudal agenesis
    - Caudal regression syndrome
    - Congenital deafness
    - Hydrocephalus
    - Mental retardation
    - Microcephaly
    - Microphthalmia
    - Myelomeningocele
    - Spina bifida
  - Cardiovascular malformations
    - Aortic stenosis
    - Coarctation of the aorta
    - Patent ductus arteriosus
    - Pulmonary stenosis
    - Truncus arteriosus
    - Ventricular septal defect
  - Musculoskeletal
    - Clinodactyly of the fifth finger
    - Congenital dislocation of the hip
    - Flexion deformities of the fingers
    - Syndactyly
    - Talipes equinovarus
  - Miscellaneous
    - Bipartite uterus
    - Cleft palate
    - Epicanthic folds
    - Hymenal atresia
    - Hypertelorism
    - Low-set ears
    - Macroglossia
    - Macrosomia
    - Micrognathia
    - Pigmentary defects of iris and hair
    - Preauricular pit
    - Short neck
- Urinary malformations associated with multicystic dysplastic kidney include the following:
  - Bladder wall diverticulum
  - Contralateral renal agenesis
  - Dysplasia
  - Hypoplasia
  - Crossed fused renal ectopia
  - Cystic dysplasia of the testis
  - Ectopic kidney
  - Fibromuscular dysplasia
  - Horseshoe kidney
  - Patent urachus
  - Seminal vesicle abnormalities
  - Ureterocele
  - Contralateral ureteropelvic junction obstruction has been reported in 7–12 % of patients.
  - Posterior urethral valves
  - Contralateral vesicoureteral reflux is reported in 4–19 % of patients.
- In children older than 2 years, 72 % of patients with multicystic dysplastic kidney showed compensatory growth of the contralateral kidney.

5.8 Clinical Features

- Most cases of multicystic dysplasia of the kidney (MCDK) are detected during fetal ultrasonography and are reported as early as 15 weeks' gestation.
- An abdominal mass in the flank of an otherwise healthy newborn was the most common clinical presentation of unilateral multicystic dysplastic kidney.
- The abnormal kidney is palpable in only 13–22 % of patients.
- The mass is usually mobile, ballotable, and irregular in shape, nontender, and might transilluminate.
- Multicystic dysplastic kidney is usually asymptomatic and can remain undetected into adulthood.
- Abdominal or flank pain and respiratory distress are uncommon symptoms because of the pressure effect of the abnormal kidney.
- Multicystic dysplastic kidney might be discovered during an investigation for urinary tract infection (UTI), voiding dysfunction, or hypertension. Multicystic dysplastic kidney may also be discovered when diagnostic imaging studies are performed to investigate a nonurinary problem.
- Bilateral multicystic dysplastic kidney usually results in stillbirth or death within the first few days of life; however, an infant with bilateral multicystic dysplastic kidney who survived for 17 days was reported.
- Bilateral multicystic dysplastic kidney is usually associated with oligohydramnios, amnion nodosum, pulmonary hypoplasia, and Potter facies.
- Infants with bilateral multicystic dysplastic kidney who survive have renal failure from birth and require dialysis from the first day of life.

5.9 Investigations

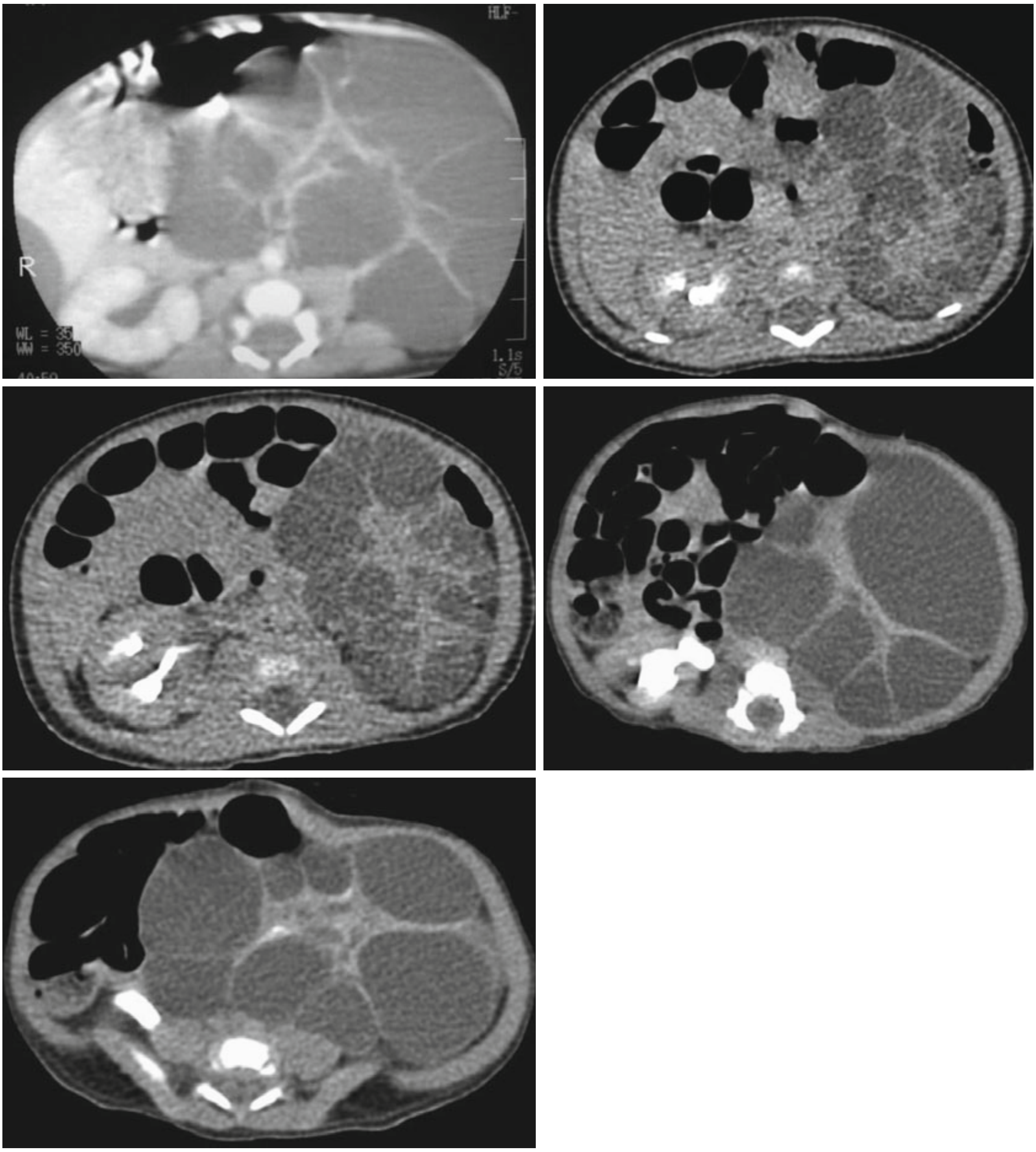
- CBC
- Serum electrolytes, BUN and creatinine
- Urine analysis and culture
- Abdominal radiograph may show a soft tissue density with displacement of the bowels in those with enlarged MCDK. Rarely, ring like calcifications of the cyst walls may be seen on plain radiographs.
- Abdominal ultrasound is the preferred initial examination.
  - Ultrasonography is an excellent diagnostic test for MCDK, with a high degree of confidence.
  - Currently, the majority of MCDK cases are diagnosed by antenatal ultrasound examination.
  - Abdominal ultrasound is accurate, and it does not require sedation, radiation, and can be repeated easily.
  - The cysts of MCDK may become enlarged, may shrink, or may involute during fetal life.
  - Bilateral MCDK may occur with oligohydramnios as a result of poor urine production.
  - In patients with a prenatal diagnosis of MCDK, a postnatal ultrasound should be done prior to discharge to differentiate MCDK from hydronephrosis.
  - Abdominal ultrasounds characteristically show:
    - Hypoechoic cysts of variable sizes and shapes
    - Interfaces between cysts
    - A nonmedial location of large cysts
    - The absence of an identifiable renal sinus
    - Lack of communication between cysts
    - Minimal surrounding parenchyma
  - An obstructive uropathy with little renal parenchyma can mimic MCDK, but radionuclide studies can provide confirmation of the diagnosis.
  - The presence of a kidney shape and/or a large cystic structure in the medial portion of the kidney on ultrasound evaluation are more suggestive of hydronephrosis than MCDK. In MCDK, the cysts do not communicate, while in hydronephrosis there is communication with the central renal pelvis.
  - The autosomal recessive polycystic kidney disease (PCKD) is not usually mistaken for MCDK, as the cysts in PCKD are too small

to be visualized on sonograms, and the parenchyma is generally homogeneously hyperechoic.

- Radionuclide scan:
  - Radionuclide scan is useful in differentiating an obstructed functioning kidney from MCDK.
  - Radionuclide scan may be necessary if ultrasonography does not reveal the classic features of multicystic dysplasia of the kidney.
  - Radionuclide scan is useful in estimating the function of the involved kidney.
  - Technetium-99m (^{99m}Tc) mercaptoacetyltriglycine (MAG-3) and ^{99m}Tc dimercaptosuccinic acid (DMSA) studies can demonstrate lack of function in the affected kidney, but MAG-3 and DTPA studies can also provide information regarding drainage in an obstructed hydronephrotic kidney.
  - The hydronephrotic form of MCDK can mimic ureteropelvic junction obstruction, and radionuclide scanning is necessary to confirm the diagnosis.
  - On radionuclide scan, the area of the MCDK appear as a photopenic region that represents displaced tissue with background activity only.
  - DMSA renal scanning demonstrates absence of function in the kidney with multicystic dysplastic kidney.
- Voiding cystourethrography (VCUG):
  - This is useful in patients with MCDK to evaluate for vesicoureteral reflux (VUR).
  - VUR could lead to reflux nephropathy in the contralateral solitary kidney.
  - Current recommendations for patients with unilateral multicystic dysplastic kidney include evaluation of the contralateral kidney for VUR by VCUG.
  - VUR has been reported in 4–19 % of contralateral kidneys but it is usually low grade and resolves in early life.
  - VCUG may be deferred, unless abnormal ultrasonography findings in the contralateral kidney or ureter and/or a history of UTI are noted.
- Intravenous pyelography (IVP):
  - This is not usually necessary; however, if multicystic dysplastic kidney involves only the upper or lower segment of a duplicated system, an IVP might reveal a small but functional ipsilateral kidney with an incomplete and possibly dilated calyceal system.
- Abdominal CT-scan is also rarely done to diagnose MCDK (Figs. 5.12, 5.13, 5.14, 5.15, and 5.16).
  - Abdominal CT-scan show the typical multicystic appearance of MCDK with little or no parenchyma. Cyst wall calcification may be seen also.
  - If a contrast-enhanced CT scan is performed, there is no excretion seen.
- Retrograde pyelography is rarely done to demonstrate an atretic or absent ureter. This is usually done through a cystoscope.
  - Retrograde pyelography demonstrates a ureter that terminates blindly below the ureteropelvic junction.
- Abdominal MRI:
  - This show the typical multicystic appearance of MCDK with little or no parenchyma.

5.10 Treatment

- In the past, nephrectomy was often performed to establish the diagnosis.
- Currently, the role of nephrectomy in multicystic dysplasia of the kidney (MCDK) is controversial.
- The indications for nephrectomy in multicystic dysplasia of the kidney are:
  - Large multicystic dysplastic kidney causing abdominal or flank pain
  - Urinary tract infection (UTI)
  - Hypertension
  - Renal malignancy
- Multicystic dysplasia of the kidney can attain a large size and cause significant abdominal or flank discomfort and pain and these should be removed.
- Urinary tract infection involving the multicystic dysplastic kidney calls for its removal.



Figs. 5.12, 5.13, 5.14, 5.15, and 5.16 Multiple CT-scan showing multicystic dysplastic kidneys. Note the different sizes of the cysts which are noncommunicating

- Multicystic dysplastic kidney complicated by hypertension is an indication for nephrectomy.
- The presence of a renal malignancy based on diagnostic imaging is an indication for nephrectomy.
  - Some concern surrounds the possibility that the intervening stroma of a kidney affected by multicystic dysplastic kidney might provide a focus for malignant degeneration.
  - No increased risk of Wilms tumor has been demonstrated in patients with multicystic dysplastic kidney.
  - Some authors recommend nephrectomy only in patients who do not show involution

  over a defined period, such as the first 5 years of life.
  - The role of laparoscopic nephrectomy for multicystic dysplastic kidney is controversial.
- It is recommended that children with multicystic dysplastic kidney should undergo renal ultrasonography every 6–12 months until age 5 years or until involution is noted.
- Patients with multicystic dysplastic kidney and contralateral VUR should receive antibiotic prophylaxis during infancy and early childhood. It has been estimated that:
  - Spontaneous resolution of VUR occurred in 89 % of patients with grades I and II VUR
  - Spontaneous resolution of VUR occurred in only 50 % of patients with grades III and IV VUR.
- Abdominal ultrasounds are done during follow ups to ensure the healthy kidney is functioning properly and that the unhealthy kidney is not causing adverse effects.
- It has been recommended that patients with multicystic dysplastic kidney should be followed-up lifelong whether or not involution has occurred or a nephrectomy has been performed. Long-term follow-up of patients with a single kidney revealed:
  - Hypertension in 27–47 % of patients
  - Proteinuria in 23–47 % of patients
  - Renal insufficiency in 3–13 % of patients

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6 Congenital Ureteral Anomalies

Congenital Ureteral Anomalies

- Duplex (duplicated ureters) (Fig. 6.1)
- Ectopic ureter
- Ureterocele
- Mega ureter
- Vesicoureteral reflux (VUR)

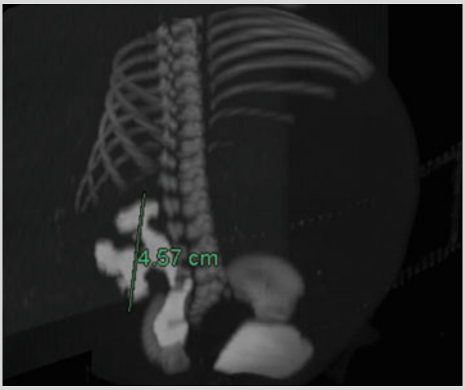

Fig. 6.1 A reconstruction picture showing duplex ureters

- The outcome of ureteral anomalies chiefly depends on the presence or absence of obstruction and/or infection, and associated renal injury.
- In the absence of these, no treatment may be necessary, especially in the case of:
  - Isolated ureteral duplication anomalies
  - Low-grade VUR
  - A small orthotopic ureterocele
  - A nonobstructed, nonrefluxing primary mega ureter

6.1 Etiology

- The ureter develops around the fourth and sixth week of gestation.
- The ureter develops from a ureteral bud, the early precursor of the ureter, branches off from the caudal portion of the Wolffian (mesonephric) duct.
- The ureter grows cranially and caudally.
- The cranial portion of the ureteral bud joins with the metanephric blastema and begins to induce nephron formation.
- The bud subsequently branches into the renal pelvis and the calyces and induces nephron formation.
- The caudal portion of the ureteral bud along with the mesonephric duct are incorporated into the cloaca as it forms the bladder trigone.
- Ureteral anomalies develops as a result of alterations in:
  - Ureteral bud number
  - Ureteral bud position
  - Time of ureteral development
- Incomplete (partial) ureteral duplication, with a single ureteral orifice and bifid proximal ureters:
  - This results from early branching of a single ureteral bud

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A.H. Al-Salem, *An Illustrated Guide to Pediatric Urology*, DOI 10.1007/978-3-319-44182-5_6

- Complete ureteral duplication:
  - This results from an accessory ureteral bud.
  - Complete duplication occurs when two separate ureteric buds arise from a single Wolffian duct.
  - According to the Weigert-Meyer rule, the future lower pole ureter separates from Wolffian duct earlier and thus migrates superiorly and laterally as the urogenital sinus grows.
  - The result is complete duplication, with the upper ureter usually protruding into the bladder more medially and inferiorly than the lower ureter.
- Ectopic termination of a single system or of the ureter of a duplex system is the result of the high (cranial) origin of the ureteral bud from the mesonephric duct.
- Ectopic ureter:
  - This results from delayed incorporation of the ureteral bud into the bladder.
  - The resulting position of the ureteral orifice is more caudal and medial or in more severe cases it inserts into one of the Wolffian duct structures.
- The ureters are paired muscular tubes that run from the renal pelvis to the bladder.
- The ureters run through three natural areas of narrowing:
  - The ureteropelvic junction
  - The crossing of the iliac vessels
  - The ureterovesical junction (UVJ)
- The UVJ may be divided into three sections:
  - The terminal portion (juxta vesical ureter)
  - The intramural portion
  - The submucosal portion (under the bladder mucosa).
- The function of the ureter is to effectively transport the urinary bolus from the minor calyces to the urinary bladder at acceptably low pressures.
- The efficiency of this function depends on adequate coaptation of the ureteral wall to propel the urinary bolus.
- If the ureter fails to propagate the peristaltic wave, the static urine distends the upper urinary tract and reduces luminal coaptation.
- Other factors that may affect ureteral transport include urinary volume and bladder pressure.

6.2 Clinical Features

- The clinical presentations of ureteral anomalies are variable and the majority are asymptomatic.
- There are no specific clinical signs associated with ureteral anomalies.
- The diagnosis is sometimes suspected on routine prenatal ultrasound.
- Some patients present with UTI, abdominal mass or hematuria.
- Children with primary mega ureters may also present with cyclic abdominal pain/flank pain, or, less commonly, acute pain crisis.
- Patients may present with a cystic mass at the urethral meatus representing a prolapsed ureterocele.
- In other patients, the diagnosis is incidental after imaging studies for unrelated symptomatology.
- Ureteral anomalies may be discovered during the evaluation of a patient with:
  - Hypertension
  - Proteinuria
  - Renal insufficiency in rare cases of severe bilateral anomalies
- Approximately 50 % of females with ectopic ureters present with constant urinary incontinence or vaginal discharge.
- In males, incontinence is never due to an ectopic ureter because the ectopic ureter never inserts distal to the external urethral sphincter.
- Rarely, an ectopic ureteral insertion may present with recurrent epididymitis in pepubertal boys.
- Post pubertal males with ectopic ureters most commonly present with chronic prostatitis and painful intercourse and ejaculation.

6.3 Investigations and Diagnosis

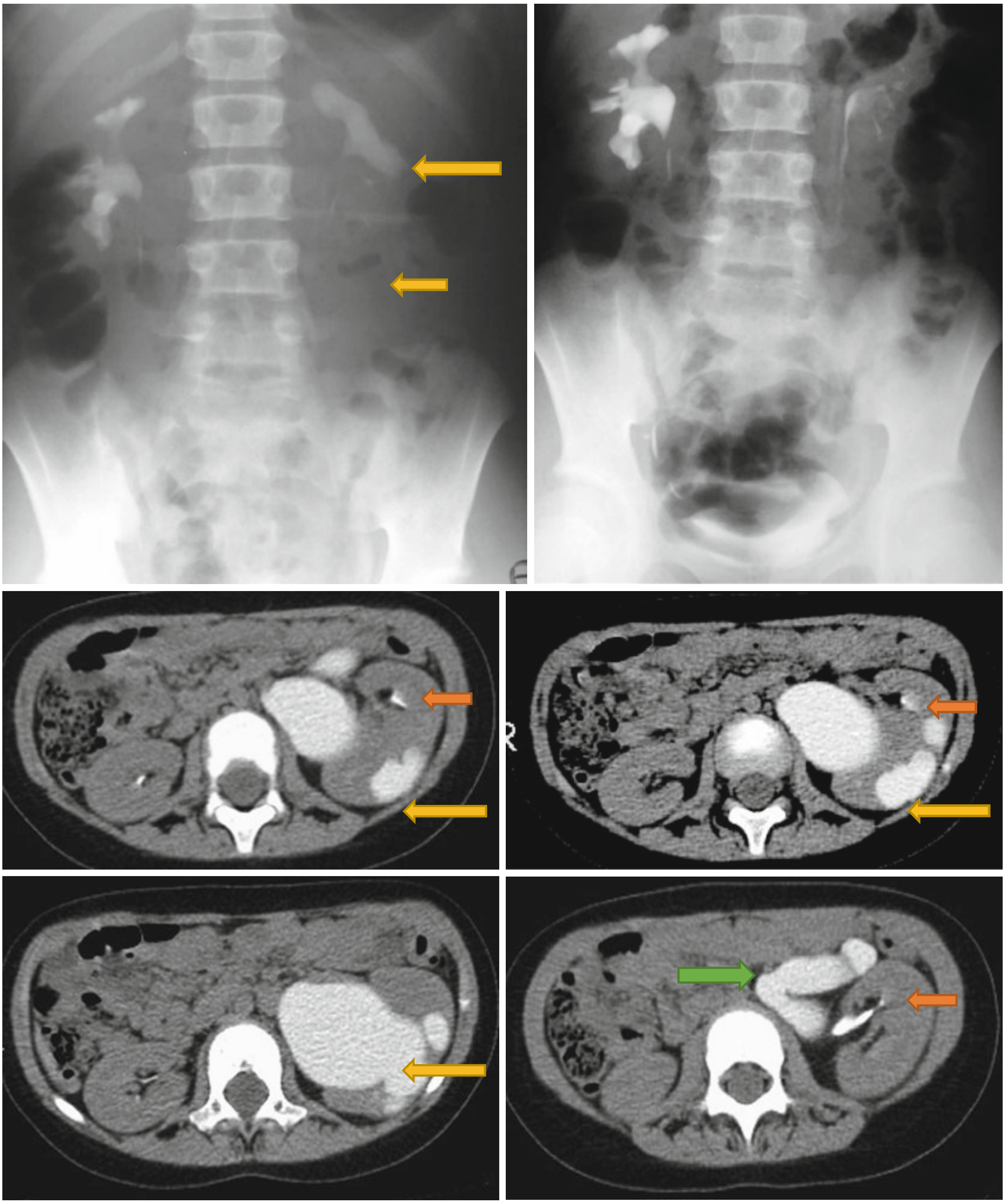
- Urinalysis and urine culture are important in children presenting with unexplained fever.
- The diagnosis of UTI should prompt further radiological evaluation to identify urological anomalies.

- Renal and bladder ultrasound:
  - This is a first-line imaging study to evaluate the upper and lower urinary tract.
  - Ultrasound evaluation of upper urinary tract anomalies include ureteral duplication, dilatation of collecting system, character and thickness of the renal parenchyma.
  - Ultrasound evaluation of lower urinary tract anomalies include bladder wall thickness, ureterocele, bladder diverticulum, posterior urethral dilatation, and degree of bladder emptying.
- Voiding cystourethrogram (VCUG):
  - This is valuable for evaluation of the bladder and urethra.
  - This includes evaluation of:
    - VUR
    - Bladder diverticulum
    - Ureterocele
    - Bladder trabeculations and bladder emptying
    - Urethral anatomy during voiding
    - The ureters if VUR is present
- Diuretic nuclear renography:
  - This is an excellent study to evaluate:
    - The differential renal function
    - Cortical scars
    - Drainage efficiency of the dilated collecting system based on washout times
- Intravenous pyelogram (IVP):
  - This study has been largely replaced by ultrasound and nuclear renography.
  - IVP delineates anatomy of the kidney, collecting system, ureter and urinary bladder.
  - It also provides subjective estimation of relative renal function.
- MR urography (MRU):
  - This provides excellent anatomic and functional evaluation of the renal parenchyma, collecting system and vasculature without exposure to radiation.
  - MRU is sensitive to motion artifact and necessitates anesthetic sedation of young children.
- Urodynamic studies:
  - This is valuable to assess voiding and bladder function in those with suspected neurogenic bladder.
- Cystoscopy, vaginoscopy, and retrograde pyelogram are endoscopic procedures that allow direct visualization of the genital and lower urinary tracts and may include radiographic visualization of the upper urinary tract (e.g. retrograde pyelogram).
- Pressure-perfusion studies (Whitaker test):
  - This measure differential pressures of the renal pelvis and the bladder
  - It may be useful in evaluating equivocal urinary tract obstruction
  - It is invasive and depends on percutaneous placement of a catheter
  - It is seldom used in the modern era of nuclear renography

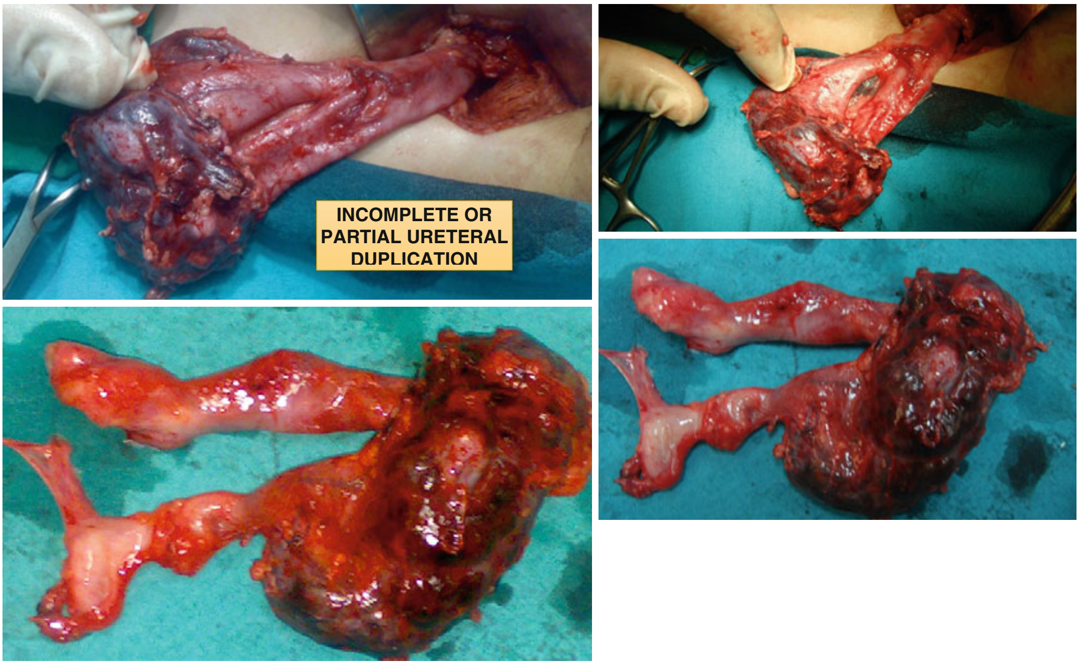
6.4 Duplex (Duplicated) System

6.4.1 Introduction

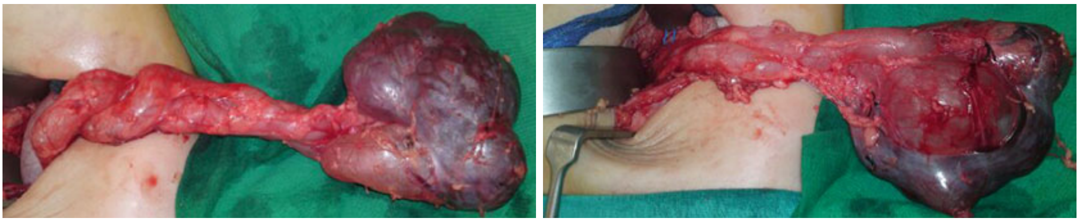
- A duplex collecting system is one of the most common congenital urinary tract abnormalities.
- It is characterized by an incomplete fusion of upper and lower pole moieties resulting in a variety of complete or incomplete duplications of the collecting system.
- A duplex (duplicated) collecting systems can be defined as renal units containing two pyelocaliceal systems that are associated with a single ureter or with double ureters.
- The two ureters empty separately into the bladder or fuse to form a single ureteral orifice.
- Duplex collecting systems can be unilateral or bilateral and can be associated with a variety of congenital genitourinary tract abnormalities (Figs. 6.2, 6.3, 6.4, 6.5, 6.6, and 6.7).
- The exact incidence of ureteral duplication is not known but an incidence as high as 8 % in children was reported.
  - Incomplete ureteral duplication was reported in approximately 1 in 25 individuals (Figs. 6.8, 6.9, 6.10, and 6.11).
  - Complete ureteral duplication was reported in approximately 1 in 125 individuals (Figs. 6.12 and 6.13).



Figs. 6.2, 6.3, 6.4, 6.5, 6.6, and 6.7 Intravenous urography and CT urography showing duplex ureters. In the intravenous urography pictures, each ureter is draing one renal unit. There is an associated hydronephrosis in the upper renal unit. The lower renal unit is normal. Note also on the CT urography the associated hydronephrosis and hydroureters in the lower renal unit while the upper renal unit is normal



Figs. 6.8, 6.9, 6.10, and 6.11 Clinical intraoperative photographs showing duplex ureters. Note the complete and partial ureteral duplications



Figs. 6.12 and 6.13 Clinical intraoperative photographs showing complete ureteral duplication. Note the associated dysplastic kidney

- In patients with complete duplication on one side, there is a 40 % chance of finding complete duplication on the other side.
- Approximately 10 % of siblings may also be affected by complete duplication.
- Duplex collecting systems are seen in 0.7 % of the normal adult population and in 2–4 % of patients investigated for urinary tract symptoms.
- The duplicated ureters can be:
  – Bifid ureters (partial or incomplete duplication)
    - The two ureters fuse together and insert distally as a single ureter into the urinary bladder.
  – Complete duplication where the two ureters empty separately into the urinary bladder.
    - The upper ureter is more likely to be associated with ectopic insertion, ureterocele, and/or obstruction.
    - Caudal or medial ectopia describes the ureteral orifice when located at the proximal lip of the bladder neck or more distal.
    - The lower ureter is more frequently associated with VUR.
    - The upper pole is one of the components of the duplex kidney.

    - The upper pole ureter drains the upper pole of a duplex kidney.
    - Similarly, the lower pole of the kidney is drained by the lower-pole ureter.
- Most patients are asymptomatic, with urinary tract abnormalities being detected incidentally on imaging studies performed for other reasons.
- These anomalies are commonly asymptomatic and considered an anatomical variant.
- Ureteropelvic obstruction is more common when a duplex kidney exists and can be inherited in an autosomal dominant pattern.
- Congenital renal anomalies in patients with classic bladder exstrophy occur in 2.8 % of patients.
- The most common anomaly is a duplicated collecting system, which occurs in approximately 1.3 % of patients.
- Duplex collecting systems may be complicated by:
  – Vesicoureteral reflux
  – Obstruction
  – Ureterocoele
- Each of these complications may have adverse effects on the ipsilateral kidney.
- A patient's duplex kidney is almost always more elongated than his/her nonduplex kidney.
- The kidney may be enlarged when hydronephrotic and can be associated with rotational anomalies.
- Magnetic resonance urography (MRU) may be used as the primary diagnostic method for assessing a duplex ectopic ureter, as well as the complications associated with duplex kidneys.
- If vesico-ureteral reflux exists, the presence of an ectopic ureter in a nonfunctioning moiety can best be demonstrated using a voiding cystourethrogram.
- Antegrade pyelography is useful in patients with hydronephrosis, to demonstrate the presence of a second ureter and to determine the level of ureteric termination.
- Computed tomography (CT) scanning with contrast is valuable in the evaluation of an intravesical ureterocele, either orthotopic or ectopic.
- Scintigraphy is useful in the assessment of relative renal function and in the detection of renal scars. Scintigraphy can reveal differential functioning. However, if the functioning is markedly depressed, imaging is limited.
- In the absence of obstruction and/or VUR, ureteral duplication anomalies require no specific therapy.
- Symptomatic patients usually have complete ureteric duplication in which the ureters are prone to develop obstruction, reflux, and infection.
- Duplication anomalies with associated pathology, such as VUR or obstruction, require appropriate medical therapy and possible surgical correction.

6.4.2 Classification

- Duplex collecting system or duplex kidney anomalies can be classified into the following categories depending on the level or lack of fusion:
  – Duplex kidney:
    - The duplex kidney has a single renal parenchyma that is drained by two separate pelvicalcyeal systems
  – Duplex collecting system: The kidney has two pyelocaliceal systems and is associated with a single ureter or with a bifid ureter (a partial duplication) or, in the case of a complete duplication, with two ureters (double ureters) that drain separately into the urinary bladder.
  – So, a duplex collecting system is a duplex kidney draining into:
    - Single ureter: Duplex kidneys and duplication pelvicalyceal systems uniting at the pelviureteric junction (PUJ)
    - Bifid ureter (ureter fissus): two ureters that unite before emptying into the bladder
    - Double ureter (complete duplication)
  – Bifid collecting system:
    - This refers to a duplex kidney with the two separate pelvicalyceal collecting systems uniting at the PUJ or as bifid ureters.

    - Two pelvicalyceal systems join at the ureteropelvic junction (bifid pelvis), or two ureters join before draining into the urinary bladder (bifid ureters).
  - Double/duplicated ureters (or collecting system):
    - This is characterized by two ureters that drain separately into the bladder or genital tract.
    - Two ureters open separately into the renal pelvis superiorly and drain separately into the bladder or genital tract.
    - Upper and lower pole ureters drain a duplex kidney’s upper and lower poles, respectively.
- As a result of these anatomic abnormalities:
  - The duplicated ureters may be seen extending a variable distance down to the urinary bladder.
  - Obstruction of the upper pole moiety down to the bladder may be seen, often associated with a ureterocoele.
  - Vesicoureteral reflux into the lower pole moiety may be seen. This is often due to distortion in its insertion by an associated ureterocoele.
  - Ectopic insertion of the upper pole moiety e.g. into the prostatic urethra in males or vaginal vault in females.
  - If reflux is significant, evidence of reflux nephropathy may be evident.

6.4.3 Clinical Features

- Most duplicated systems are asymptomatic and diagnosed incidentally.
- Duplex collecting system may be complicated by infection, vesicoureteral reflux or obstruction.
- Occasionally, hydronephrosis can be severe enough to result in flank discomfort, pain or even a palpable mass.

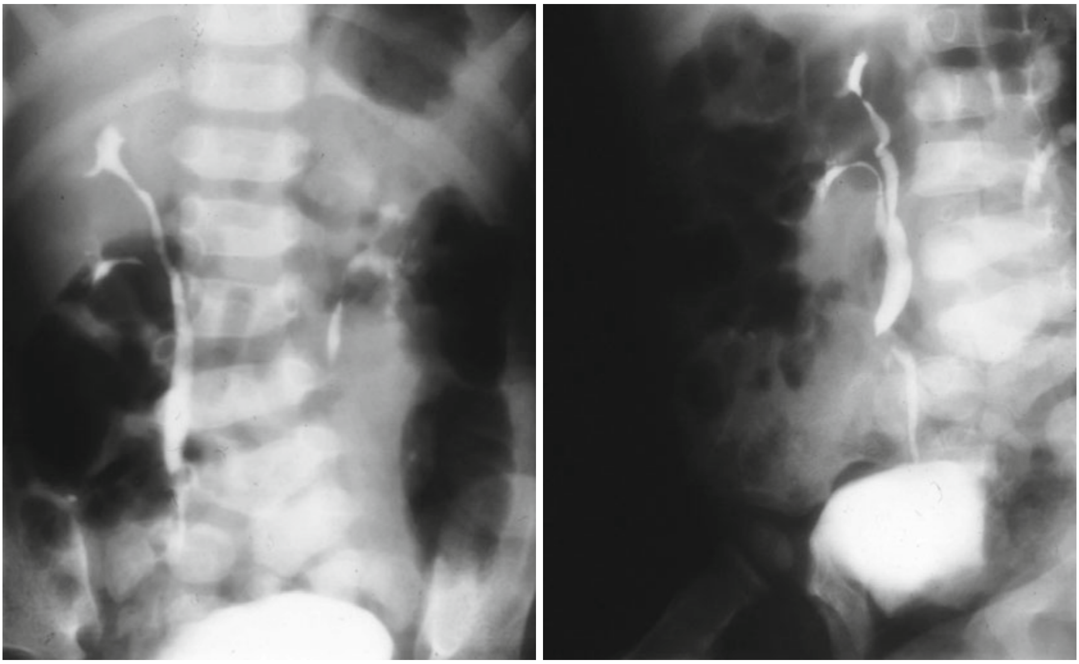
Classification of Duplex Collecting System

- Duplex kidney: Two separate pelvicalyceal system draining a single renal parenchyma.
- Duplex collecting system: A duplex kidney draining into:
  - A single ureter: Duplex kidney with pelvicalyceal system uniting at the pelviureteric junction.
  - Bifid ureters: Two ureters that unite before emptying into the urinary bladder.
  - Double ureters (Complete duplication)
- Bifid collecting system: A duplex kidney with the two separate pelvicalyceal collecting system uniting at the pelviureteric junction or as bifid ureters (Incomplete ureteral duplication).
- Double/Duplicated ureters: Two ureters that drain separately into the urinary bladder or genital tract (Complete ureteral duplication).

- These are seen in patients with completely duplicated ureters.
- Duplication can be variable.
- At one end of the spectrum, there is merely a duplication of the renal pelvis, draining via a single ureter.
- At the other extreme, two separate collecting systems drain independently into the bladder or ectopically.
- Duplex systems may be unilateral or bilateral and can be associated with a variety of other congenital abnormalities of the urinary tract.
- Duplex systems can be associated with Fanconi anemia.

6.4.4 Investigations

- Intravenous urography (IVU) (Figs. 6.14 and 6.15):
  - This can demonstrate both collecting systems, but a poorly functioning system may not excrete contrast and will not be visualized.
  - In such a situation, the functioning lower pole moiety will be inferiorly displaced,



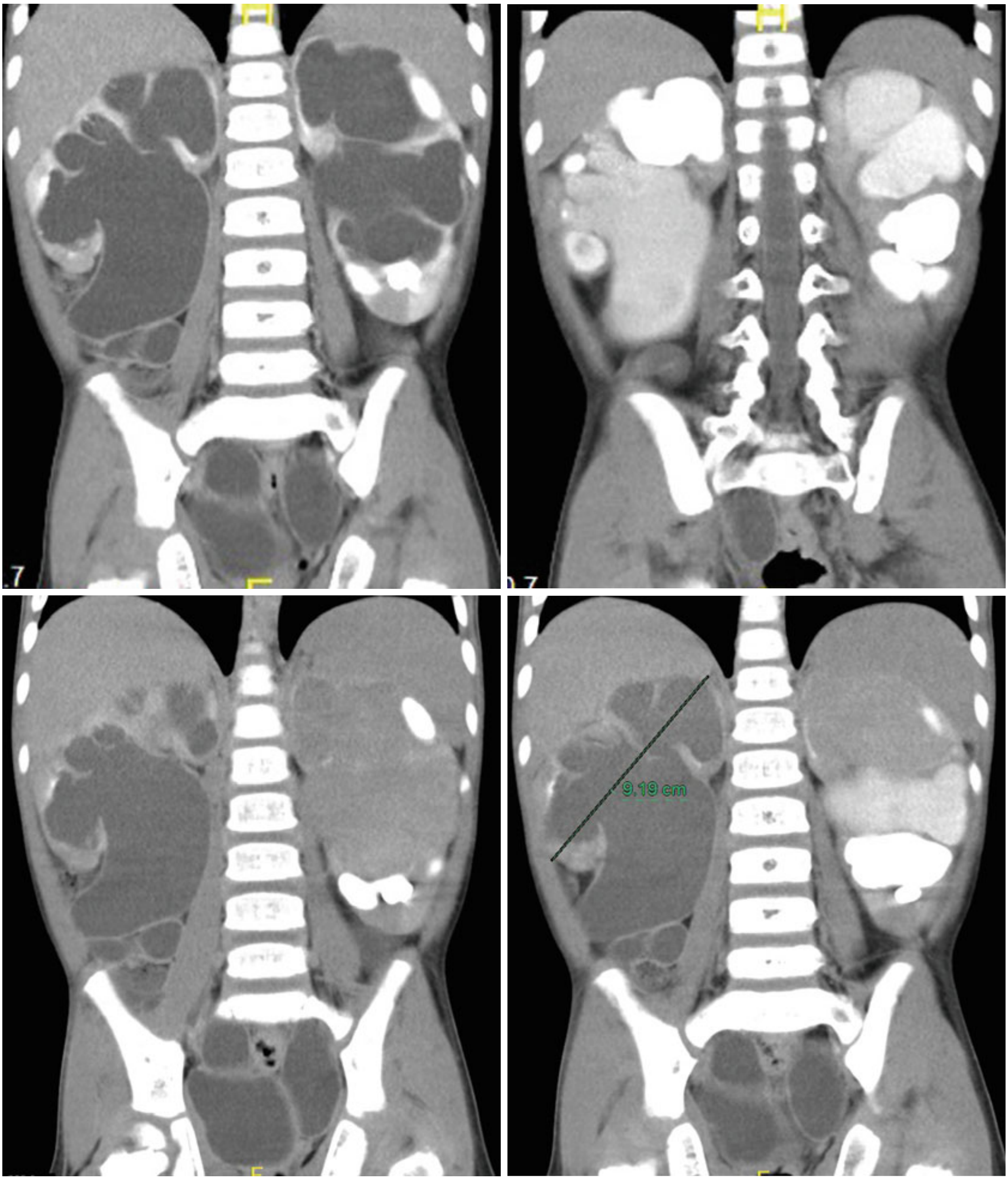
Figs. 6.14 and 6.15 Intravenous urography showing partial (incomplete) ureteral duplication on the right side

  taking on the so-called "drooping lily appearance".
  - This may be confused with an upper pole mass or cyst.
  - A patient's duplex kidney is usually longer than his/her nonduplex kidney.
  - The parenchymal thickness of one of the poles of the duplex kidney is less than that of the other pole.
  - The calyces are asymmetric
  - An ectopic, upper pole ureteric insertion can produce a nonopacified segment. This mass effect results in the "drooping lily" sign with the depression of the lower pole pelvicaliceal system.
  - If the lower pole of the duplex kidney is functioning poorly or not at all, the lower pole collecting system may not opacify, and no discernible parenchyma will surround it (nubbin sign). The kidney's appearance may consequently resemble that of a nonduplex kidney with a lower polar mass or renal infarct.
  - A reduction in the number of calyces, the depiction of a portion of the collecting system, and the presence of a straight inferior border help to differentiate a duplex collecting system from a renal mass.
  - Anomalies of the ureter, such as partial or complete ureteral duplication, may be demonstrated.
- Abdominal and pelvic ultrasound:
  - Ultrasound is useful when the duplex system is associated with obstruction/hydronephrosis.
  - Ultrasound is also useful in detecting associated ureterocele.
  - With the use of ultrasound it may be difficult to differentiate between partial and complete duplication.
  - The duplex kidney appears as two central echo complexes with intervening renal parenchyma.
  - Hydronephrosis at one pole is suggestive of a duplex kidney.
  - Although hydronephrosis can occur at either pole, it is more common in the upper pole.
  - Occasionally, two distinct collecting systems and ureters can be observed on ultrasonographic images.

  - Differentiating an atrophied lower pole moiety of a duplex kidney (nubbin) from other renal masses is difficult.
  - The nubbin of tissue from the atrophied lower pole of a duplex kidney cannot be confidently differentiated from other masses.
- CT urography:
  - CT urography is able to delineate essentially all duplex abnormalities especially if reconstruction images are made.
  - The intervening renal parenchyma in a duplex kidney lacks a collecting system and major vessels, and because of this it is described as having a "faceless kidney" appearance.
  - A duplicated renal collecting system can be suspected if a faceless kidney is identified.
  - CT scan can help to determine if an obstruction exists and can aid in assessing the renal parenchyma thickness.
  - CT scan can also help to determine if the insertion of the duplex ureter is intravesical or extravesical.
  - CT scan can demonstrate the collecting system in the nubbin or the mass effect of tissue at the pole.
  - CT scan is superior to ultrasonography and excretory urography in diagnosing the lower pole nubbin.
- Nuclear scan:
  - Renal scintigraphy is useful to evaluate renal function, particularly when planning corrective surgery.
  - Renal scintigraphy is less useful to identify non-obstructed duplex systems.
  - Duplex kidneys appear as two separate collecting systems on the same side of the body.
  - Scintigraphy may demonstrate reflux up the ureter in a nonfunctioning duplex kidney with ureteral duplication.
  - The presence of a duplex kidney and ureteral duplication, suggested by excretory urographic or ultrasonographic images, can be confirmed with scintigraphy.
  - The use of dimethyl succinic acid (DMSA) scanning to assess parenchymal function in a duplex kidney is of great value in the management of duplex kidney.
- MR urography (Figs. 6.16, 6.17, 6.18, and 6.19):
  - This may be used as a primary diagnostic method in assessing a duplex ectopic ureter and complications associated with duplex kidneys.
- An ectopic ureter extending from a poorly functioning moiety of a duplex kidney, invisible on other imaging, may be observed with MR urography
- Micturating cystourethrography:
  - The intravesical ectopic ureter of a nonvisualized moiety is better demonstrated using voiding cystourethrogram.
  - In patients with hydronephrosis, antegrade pyelography is useful for demonstrating the presence of a second ureter and for determining the level of termination.

6.4.5 Treatment and Prognosis

- An asymptomatic duplex kidney usually does not require any treatment.
- Surgical treatment is indicated in the presence of complications.
- These complications include:
  - Vesicoureteral reflux into lower pole moiety
  - Marked hydronephrosis of the upper pole moiety may have mass effect or become infected
- Antibiotic prophylaxis is given to newborns with hydronephrosis or in patients who present with urinary tract infection (UTI) until the diagnosis is made and reflux is ruled out.
- Antibiotic prophylaxis is often continued in patients with obstructed systems and in infants with dilated nonobstructed systems.
- Duplicated collecting systems with reflux are managed conservatively with antibiotic prophylaxis until the reflux spontaneously resolves or until the child is older (6–12 months), at which time surgery may be more easily accomplished.



Figs. 6.16, 6.17, 6.18, and 6.19 MRU showing bilateral duplex kidneys. Note the associated hydronephrosis and hydroureters

- In infants with duplicated systems and a well-functioning but obstructed upper-pole moiety or an obstructed ectopic single-system ureter, urinary diversion (A cutaneous ureterostomy) may be the treatment of choice until the bladder is bigger and a ureteral reimplantation with or without ureteral tailoring is more feasible.
- In infants with a duplicated system and no reflux is present in the lower-pole system, a ureteroureterostomy is an option.

- In those with upper-pole system that serves a duplicated ureterocele: typically makes up less than 30 % of the unilateral renal function, and preservation of this function is usually not critical.
  - If this poorly functioning moiety is not associated with reflux in other moieties, the best approach is excision.
  - If this poorly functioning moiety serves a decompressed ureterocele with no reflux, there is no indication for removal.
- Each ureter drains a separate renal moiety.
  - If only one moiety is involved and is poorly functioning, a single-stage nephrectomy or heminephrectomy is usually curative.
  - The likelihood that this upper-tract approach will be curative diminishes as the number of other moieties involved with either reflux or obstruction increases.
  - In this case, a lower-tract approach in which all problematic ureters can be simultaneously treated is a better option.

6.5 Ectopic Ureter

6.5.1 Introduction

- Normally the ureters drain via the internal ureteral orifice at the trigone of the urinary bladder.
- Ectopic ureter occurs when the ureter drains to an abnormally located (ectopic) orifice.
- Bilateral single-system ureteral ectopia is rare and usually coexist with other urinary tract anomalies including VUR, renal dysplasia, and rudimentary bladder development.
- Ectopic ureter (or ureteral ectopia) is a congenital malformation where the ureter, rather than terminating at the urinary bladder trigone, terminates at a different abnormal location. This abnormal location is as follows:
  - In males, the ectopic ureter drains into:
    - The lower urinary bladder
    - The posterior urethra
    - The seminal vesicle
    - The vas deferens
    - The ejaculatory duct
    - The rectum rarely
  - In females, the ectopic ureter drains into:
    - The lower urinary bladder
    - The urethra
    - The vestibule
    - The vagina.
    - The uterus or Wolffian duct remnants rarely
- An ectopic ureter is a congenital renal anomaly that occurs as a result of abnormal caudal migration of the ureteral bud during its insertion to the urinary bladder.
- Failure of separation of ureteral bud from Wolffian duct results in caudal ectopia.
- Ectopic ureter is commonly a result of a duplicated renal collecting system, a duplex kidney with two ureters.
  - One ureter drains properly to the bladder
  - The duplicated ureter presenting as ectopic
- The Weigert-Meyer rule:
  - In the case with complete duplication, the ureter draining the upper moiety inserts more medial and more inferior to the lower moiety ureter and liable for obstruction while the ureter draining the lower moiety is liable for reflux.
- Ectopic ureter can be associated with:
  - Ectopic ureter may be solitary
  - Approximately 80 % of ectopic ureters are associated with duplex kidneys
  - Ectopic ureter may be part of complex congenital anomalies
  - Hydronephrosis
  - Ureterocele
  - Renal dysplasia
  - Frequent urinary tract infections
  - Urinary incontinence (usually continuous drip incontinence).
- Ectopic ureters are found in 1 of every 2,000–4,000 patients.
- Approximately 10 % are bilateral.
- Ectopic ureters occur more frequently in females than in males (F: M 10:1 or 6:1).
- In females, more than 80 % of ectopic ureters drain duplicated systems.

- In males, most ectopic ureters drain a single system.
- Approximately 80 % of all ectopic ureters drain the upper pole of a duplex kidney.

Sites of Ectopic Ureters

- In males, the ureters always terminate proximal to the external sphincter and may be found at the:
  - Bladder neck/prostatic urethra (48 %)
  - Seminal vesicle (40 %)
  - Ejaculatory duct (8 %)
  - Vas deference (3 %)
  - Epididymis (0.5 %)
- In females, the ureters may terminate at the:
  - Bladder neck/urethra (35 %)
  - Vestibule (30 %)
  - Vagina (25 %)
  - Uterus (5 %)

- Single-system ureteral ectopia reveals widespread renal dysplasia in 90 % of affected kidneys.
- Duplicated-system ureteral ectopia reveals renal dysplasia in approximately 50 % of affected renal moieties.

6.5.2 Embryology and Pathophysiology

- In normal development, a single ureteral bud originates from the excretory duct of the pronephros and mesonephros, the mesonephric duct.
- This complex forms adjacent to the metanephric blastema, the precursor to the kidney.
- The ureteral bud migrates and rotates toward the portion of the urogenital sinus that will become the bladder and acquires a separate orifice from the mesonephric duct.
- Once in the vesical portion of the urogenital sinus, the orifice migrates superolaterally with respect to the primitive trigone as the mesonephric duct rotates caudally and medially to the part of the urogenital sinus that will become the urethra.
- The mesonephric duct eventually becomes the epididymis, vas deferens, ejaculatory duct, and seminal vesicles in the male and the Gartner's duct in the female.
- Ureteral ectopia occurs when the orifice of the developing ureter does not migrate into its proper location and takes its final position in an abnormal location.
- As a result of this, Ectopic ureters may terminate in:
  - A male vestige of the mesonephros, such as the epididymis, vas deferens, ejaculatory duct, or seminal vesicle.
  - Gartner's duct (duct of the epoophoron), the female vestigial remnant of the mesonephric duct, which resides within the muscular wall of the genital tract extending from the internal cervical os along the lateral or anterolateral vaginal wall to the hymen.
  - Nearby vestigial remnants of the Müllerian (paramesonephric) duct, such as the utriculus in the male and the upper vagina, cervix, and uterus in the female.
  - The urethra in both sexes.
- Ureteral ectopy into the rectum is rare, but it may occur when the mesonephric duct inserts posteriorly on the cloaca and/or following inappropriate division of the urorectal septum.
- The persistent common excretory duct is another rare variant of ectopia (an ectopic vas deferens opens into a ureter, culminating in a common duct that opens to the trigone).
- In ureteral duplication, two ipsilateral ureteral buds migrate separately and simultaneously toward the urogenital sinus.
- According to the Weigert-Meyer law, the lower pole ureter migrates toward the vesical portion of the urogenital sinus ahead of the upper pole ureter.
  - If both orifices reach the bladder, the orifice of the lower pole ureter is superolateral to the orifice of the upper pole ureter.
  - Ectopia of one or both ureters may occur; however, ectopia of only the upper pole

  ureter is usually present, because it is the second ureter to be incorporated onto the trigone.
  - Its late arrival to the urogenital sinus causes the migrating mesonephric duct to carry the ureter to an abnormal location outside the bladder.
- Additional anomalies of the ipsilateral or contralateral system(s) are known to occur in association with upper and/or lower pole ureteral ectopia, such as:
  - Ureterocele
  - Ureteropelvic junction obstruction
  - Renal ectopia
  - Renal dysplasia
  - Vesicoureteral reflux
- In females, the most common sites for an ectopic ureteral orifice, in decreasing order, are:
  - The urethra
  - The vestibule
  - The vagina
  - The cervix
  - The uterus
  - The Gartner's duct
  - A urethral diverticulum
- In males, the most common sites for an ectopic ureteral orifice in descending order, are:
  - The posterior urethra
  - The prostatic utricle
  - The seminal vesicle
  - The ejaculatory duct
  - The vas deferens
  - The epididymis
- In the male, the most common site is the posterior urethra, occurring in approximately 50 % of cases.
- Other sites include the seminal vesicle (approximately one-third), vas deferens, bladder neck, prostate to the level of the ejaculatory duct orifice, and epididymis.
- In males, the ectopic ureter is always above the external urinary sphincter.
- Therefore, males with an ectopic ureter do not have urinary incontinence, but typically present secondary to a prenatal diagnosis of hydroureteronephrosis or symptomatic urinary tract infection.
- The diagnosis of an ectopic ureter associated with a duplex kidney can be difficult.
- The upper pole of a duplex kidney with an ectopic ureter may be very small and poorly functioning. Its small size makes it difficult to identify on morphological imaging. As a result of its poor function, there is no or minimal uptake of the tracer when isotope studies are performed.
- Finding the opening to an ectopic ureter at cystoscopy or vaginoscopy is also difficult.

6.5.3 Clinical Features

- Ectopic ureters are often found incidentally on radiologic imaging studies.
- The symptomatology in these patients depends on the location of the ureteral orifice, its relationship to the urinary sphincter, and the competence of the bladder neck.
- In symptomatic patients, common presentations usually include:
  - Incontinence
  - Flank pain
  - Hematuria
  - Pelvic/perineal discomfort
  - Infection
  - Vaginal discharge
  - Hydrocolpos
  - Epididymo-orchitis
  - Painful intercourse
  - Ejaculatory pain
  - Prostatitis
  - Seminal vesiculitis
  - Hemospermia
  - Change in bowel habits
  - A mass in the abdomen, rectum, urethra, and vagina
  - Irritative and obstructive voiding difficulties – with or without incontinence
- In males, incontinence does not occur because ectopic ureteral orifices always terminate proximal to the external sphincter. Extremely rare, the ectopic ureter opens in the urethra just distal to the external sphincter.
- The diagnosis of ectopic ureter is difficult and even when symptoms are present, it is common

for the diagnosis of ureteral ectopia to be delayed several years.
- Clinical examination of a girl with an ectopic ureter may identify continuous dripping of urine from the introitus.
- There may be perineal irritation from continuous leaking.
- Careful targeted cystoscopy and vaginoscopy may locate an ectopic ureteric opening, but identification can be difficult and the opening easily missed.

6.5.4 Diagnosis

- Intravenous urography (IVU):
  - It can defect abnormal ureteral insertion and associated anomalies such as renal duplication.
  - In complete duplex kidney and ureter, the ectopic ureter usually drains the upper moiety and may be associated with ureterocele and obstruction.
- Voiding cystourethrogram (VCUG):
  - Usually the ectopic ureter is associated with vesico-ureteric reflux, which can be detected and graded with VCUG.
- Abdominal and pelvic ultrasound:
  - This is useful in detecting associations and complications of ectopic ureter such as duplex kidneys, hydronephrosis and ureterocoele.
- MR urography (MRU):
  - This is valuable in diagnosing ectopic ureters.
  - The ureter and its insertion may be visualized.
  - MRU is also useful in detection of other anomalies such as renal duplication, ureterocoele and vertebral anomalies.

6.5.5 Surgical Treatment

- Symptomatic ectopic ureters are treated surgically.
- The upper pole kidney associated with an ectopic ureter is usually poorly functioning and so is appropriately treated by upper pole hemi-nephrectomy.
- Complete uretrectomy may be associated with increased morbidity.
- Retaining the distal ureteric stump on the other hand carries a less than 10 % chance of re-operation for distal ureteric removal. This however will reduce the morbidity from a complete ureterectomy.
- With the recent development in minimal invasive surgery, laparoscopic hemi-nephrectomy is feasible and safe. Laparoscopic lower pole hemi-nephrectomy may be associated with risks of retroperitoneal fluid collection, loss of renal tissue and hypertension.
- Where upper pole function is preserved, an alternative to hemi-nephrectomy is ureteric re-implantation.
  - In these cases, both ureters from the duplex kidney should be re-implanted together.
  - Re-implantation, however, can be avoided by draining the upper pole into the lower pole system either with an uretero-ureterostomy or an uretero-pyelostomy.
  - Currently, laparoscopic uretero-ureterostomy and uretero-pyelostomy have been reported to be feasible and safe.
- The surgical management of systems with ectopic ureters depends on several factors:
  - The function of the involved (usually the upper pole moiety) and uninvolved renal segments.
  - Single versus duplicated systems
  - The site of terminal insertions of the ureters
  - Coexistent morbidities, such as infections, reflux, pain, infertility, incontinence, masses, and associated anatomic anomalies.
- Surgical considerations usually include:
  - Total nephrectomy
  - Upper pole partial nephrectomy
  - Ureterectomy
  - Nephroureterectomy
  - Pyelopyelostomy
  - Pyeloureterostomy
  - Ureteroneocystostomy
  - Ureteroureterostomy
  - Percutaneous decompression
  - Endoscopic incision

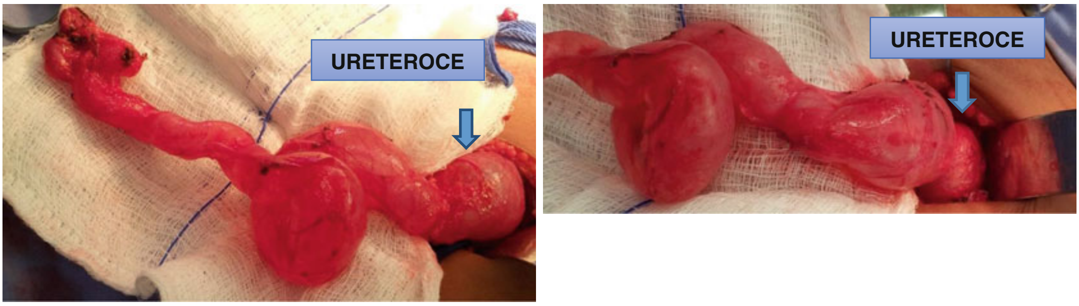
- With respect to the kidney, total and segmental renal function must be considered when contemplating nephron-sparing surgery.
- In general, the more ectopic the ureteral orifice, the more dysplastic the involved moiety of the kidney.
- The fate of the distal ectopic ureter is controversial.
  - In most cases, it can be left in situ and widely spatulated so that dissection does not compromise pelvic structures and/or the blood supply to the ipsilateral lower pole ureter of a duplicated system.
  - Primary or delayed distal stump ureterectomy may be needed in some situations:
    - Severe hydronephrosis of the remnant ureter leading to obstruction of the ipsilateral duplicated ureter.
    - Ectopic insertion into the genital or gynecologic tracts causing infertility, pain, or infection.
    - Reflux leading to recurrent infection of the ureteral stump, pain, or persistent mass.
  - Distal ectopic ureterectomy may be inevitable if there is reflux into the ectopic ureter.
  - Reflux into the ipsilateral ureter was also a risk factor, requiring secondary surgery in 40 %.
- Single system ectopic ureter:
  - About one fifth of ectopic ureters are associated with single system kidneys.
  - Single system ectopic ureters are frequently associated with other congenital problems, including anorectal, esophageal and renal tract anomalies.
  - About half of those with single system ectopic ureters ae discovered during investigation of other anomalies.
  - The remaining half present with either incontinence or infection.
  - Renal dysplasia is common but those with single system ectopic ureter are associated with kidneys with reasonable function.
  - Diagnosis of single system ectopic ureters can be difficult.
  - Micturating cystogram can demonstrate reflux in only half of the patients and initial cystoscopy can fail to identify the ectopic ureter in two-thirds of the patients.
  - If an ectopic ureter is associated with a single system and the kidney is severely dysplastic or poorly functioning, the recommended treatment is nephrectomy with partial or total ureterectomy.
  - If the involved kidney is functioning satisfactorily, the recommended treatment is ureteral reimplantation.
  - In rare instances of bilateral single-system ectopic ureters, when the bladder capacity is actually adequate for urination, bilateral ureteral reimplantation is performed.
  - If the bladder neck is poorly developed in association with the ureteral ectopia, bladder neck reconstruction (Young-Dees-Leadbetter bladder neck plasty) may be necessary.
- Bilateral ectopic ureter:
  - Bilateral ectopic ureters are a rare and distinct malformation affecting girls.
  - Neither ureter drains into the bladder which is small with a poorly developed sphincter.
  - It is possible that during development the abnormal origin of both ureteric bud results in poor mesenchymal induction of the urogenital structures. This results in failure of normal development of the bladder and the bladder neck.
  - Both the sphincter and reservoir functions of the bladder are severely affected.
  - Thus although the child may present with incontinence, ureteric re-implantation will fail to correct the incontinence and only 20 % became continent.
  - Achieving continence requires:
    - Ureteric re-implantation
    - Improvement of bladder storage
    - Improvement in bladder outlet resistance
  - Ureteric re-implantation is difficult because of the small bladder size.
  - Creating a window between a distal ureter and the bladder may, allow reasonable bladder capacity to develop and possibly avoid bladder outlet procedures and augmentation.

  - Bladder capacity may be improved with enterocystoplasty.
  - A variety of bladder outlet procedures have been described:
    - Young-Dees-Leadbetter bladder neck reconstruction
    - Kropp procedure
    - Pubovaginal sling
    - Bladder neck closure
    - Artificial urinary sphincter
- Duplex system:
  - Treatment depends on the function of the involved upper pole and whether VUR is present.
  - If function is adequate, an ureteropyelostomy (upper-pole ureter to lower-pole renal pelvis) or ureteroureterostomy (upper-pole ureter to lower-pole ureter) is performed if no VUR is noted in the lower pole ureter.
  - In patients with a functioning upper-pole system and coexisting lower-pole VUR, a common sheath ureteral reimplantation is performed.
  - If the upper-pole moiety is nonfunctional, a partial nephroureterectomy is performed and the upper-pole ureter is removed to the pelvic brim.
  - If patients have coexisting upper-pole VUR, the ureteral stump should be ligated to prevent reflux of urine into the retroperitoneum.
  - The more distal the ureter insertion, the worse the prognosis.

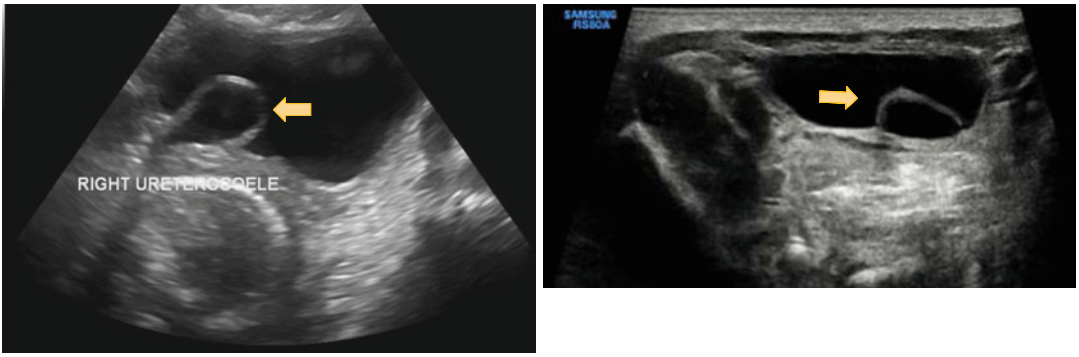
6.6 Ureterocele

6.6.1 Introduction

- A ureterocele is a congenital saccular dilatation of the distal segment of the ureter (Figs. 6.20, 6.21, 6.22, and 6.23).
- This anomaly most frequently involves the upper pole of a duplex system.
- A ureterocele contained within the bladder is called an orthotopic ureterocele.



Figs. 6.20 and 6.21 Clinical intraoperative photographs showing ureterocele. Note the associated severely dilated ureter. Note also the small atrophic dysplastic kidney



Figs. 6.22 and 6.23 Pelvic ultrasound showing right and left ureterocele

- Sometimes, the ureterocele extends beyond the bladder into the urethra.
- This is called an ectopic ureterocele.
- These patients may present with a cystic mass at the urethral meatus representing a prolapsed ureterocele.
- Ureteroceles are often associated with obstruction and VUR.
- The incidence of ureterocele is approximately 1 in 4,000 children.
- Approximately 80 % occur in females.
- Approximately 10 % are bilateral.
- Approximately 80 % are associated with duplicated collecting systems with single system ureteroceles being more common in males and adults.
- Indications for surgical interventions include:
  - Obstruction
  - Urosepsis or compromised renal function may necessitate urgent decompression prior to definitive surgical reconstruction

6.6.2 Classification

- The AAP classification of ureteroceles:
  - Intravesical ureteroceles
  - Ectopic ureteroceles
- Stephens et al. classification of ureteroceles:
  - Stenotic ureterocele (40 %):
    - This is the most common type of ureterocele.
    - The ureterocele lies within the bladder.
    - Its orifice lies within the trigone and is obstructive.
    - It corresponds to an intravesical ureterocele.
  - Sphincteric ureterocele (30 %):
    - In this form of ureterocele, a rather dilated ureter courses through the submucosa of the bladder, and adopts a more normal caliber as it travels into the urethra.
    - It has an opening at the level of the sphincter.
    - Its orifice is not narrow, but drainage from the ureterocele is impaired by contraction of the sphincter.
    - The associated ureterocele can be very large.
  - Sphincterostenotic ureterocele (6 %):
    - The ureterocele has an orifice at the level of the sphincter.
    - Its narrow orifice further impedes its drainage so that the ureterocele remains dilated and obstructs the bladder outlet.
  - Blind ureterocele (5 %):
    - This form of ureterocele extends under the trigone and into the bladder outlet.
    - No opening is identifiable.
    - The dilated ureterocele can cause severe bladder outlet obstruction.
  - Non-obstructive ureterocele (5 %):
    - This type of ureterocele lies entirely within the bladder, and has a large opening which does not impede drainage of the ureterocele.
  - Caecoureterocele (5 %):
    - This form of ureterocele extends submucosally into the urethra.
    - The orifice of the ureterocele lies more proximally either in the urethra or the bladder.
    - A "tongue" of submucosal ureterocele lies caudal to the opening.
    - If its opening is small, filling of the ureterocele may obstruct the bladder outlet.
    - If the ureterocele has a large opening (either naturally or iatrogenically) the tongue of the caecoureterocele will fill by reflux during voiding and may obstruct the urethra.

Classification of Ureteroceles

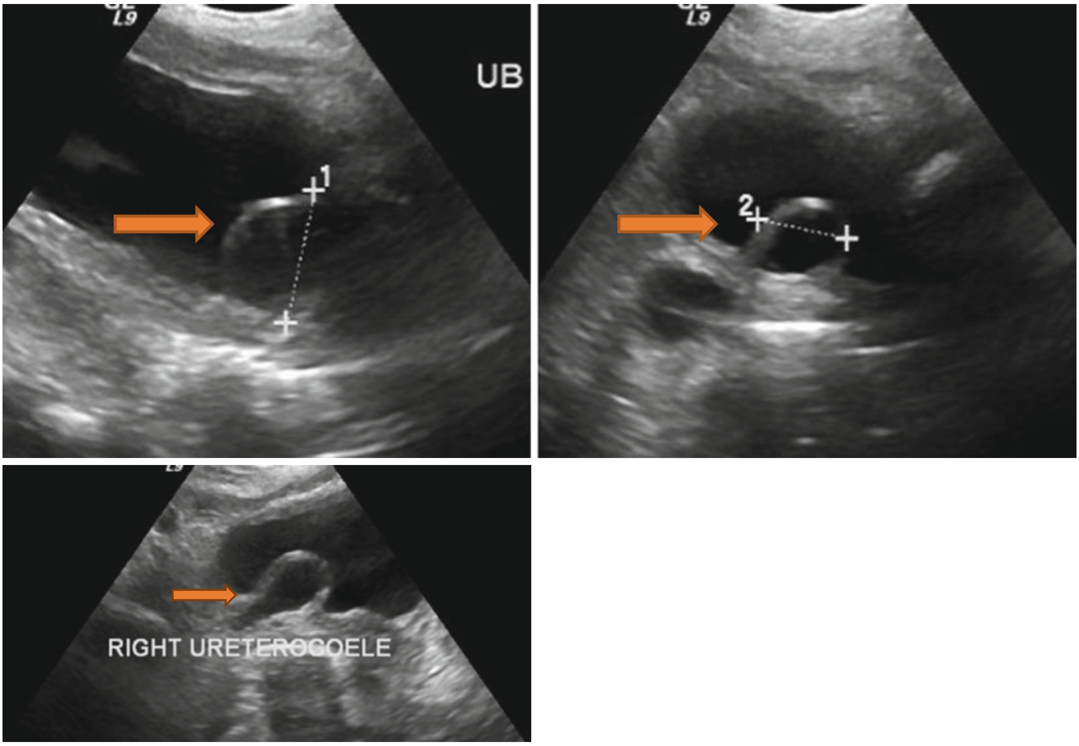
- The AAP classification:
  - Intravesical ureterocele
  - Ectopic ureterocele
- The Stephens et al. classification:
  - Stenotic ureterocele (40 %)
  - Sphincteric ureterocele (30 %)
  - Sphincterostenotic ureterocele (6 %)
  - Blind ureterocele (5 %)
  - Non-Obstructive ureterocele (5 %)
  - Caecoureterocele (5 %)

6.6.3 Clinical Features

- The exact incidence of ureterocele is not known and at post-mortem, ureterocele was estimated to occur 1 in 500–4,000.
- In patients with duplex kidneys, ureterocele is found in 5–20 %.
- With the wide spread use of antenatal ultrasound, half to three quarters of ureteroceles are detected antenatally.
  - It is common for ureteroceles to obstruct the upper pole of the affected kidney from which they have arisen.
  - The lower pole ureter may be obstructed by the dilated upper pole ureter.
  - A ureterocele that obstructs the bladder outlet will affect the contralateral kidney as well.
- Ureteroceles may be associated with vesicoureteral reflux which affect the ipsilateral lower pole in half, and the contralateral kidney in a quarter.
- Abnormal bladder function is common in children with ureterocele.
  - More than half will have abnormally large bladders, and residual volumes are common.
  - Stones have been observed in a large proportion of adult patients presenting with ureterocele.

6.6.4 Investigations and Diagnosis

- The aims of investigating patients with ureteroceles are:
  - To confirm the diagnosis
  - To determine its structure (intravesical or ectopic)
  - To identifying coexisting pathology:
    - VUR
    - Lower pole and bladder outlet obstruction
- Abdominal and pelvic ultrasound (Figs. 6.24, 6.25 and 6.26):
  - The ureterocele and its associated dilated ureter and upper pole are usually identified on ultrasound.



Figs. 6.24, 6.25, and 6.26 Abdominal and pelvic ultrasounds showing right ureterocele

  - It is important not to confuse a dilated distal ureter that is adjacent to the bladder with a ureterocele.
  - A ureterocele that is collapsed may be missed at the time of ultrasound scanning.
- Micturating cystourethrogram (MCUG):
  - This is an important investigation in patients with suspected ureterocele.
  - It identifies its size, site and the relationship of the fundus and base of the ureterocele to the bladder neck and urethra, indicating possible bladder outlet obstruction (Fig. 6.27).
  - MCUG is useful in detecting associated VUR.
  - Care should be taken that an everted ureterocele is not miss-diagnosed as a paraureteric diverticulum.

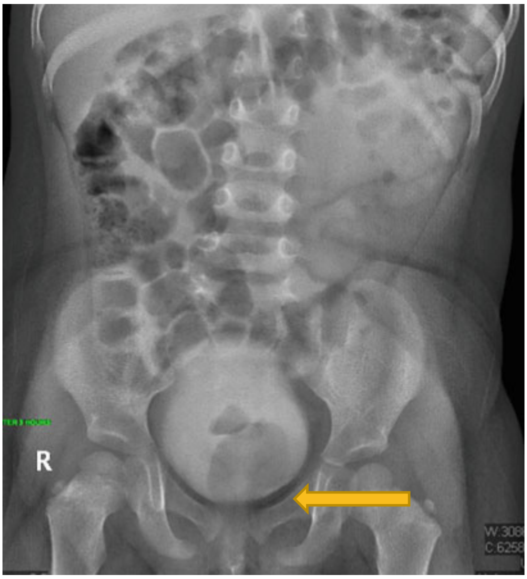
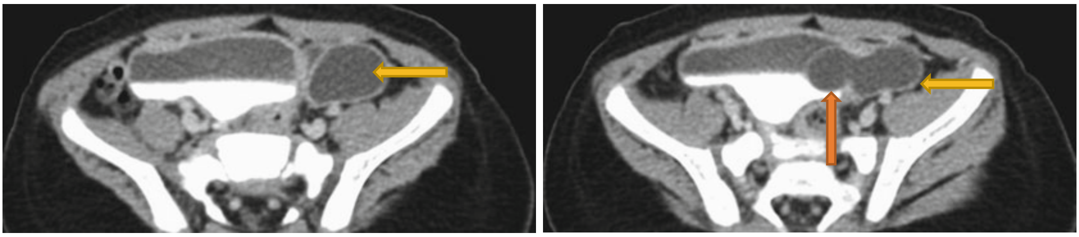


Fig. 6.27 A delayed film of MCUG showing a filling defect in the bladder representing a ureterocele

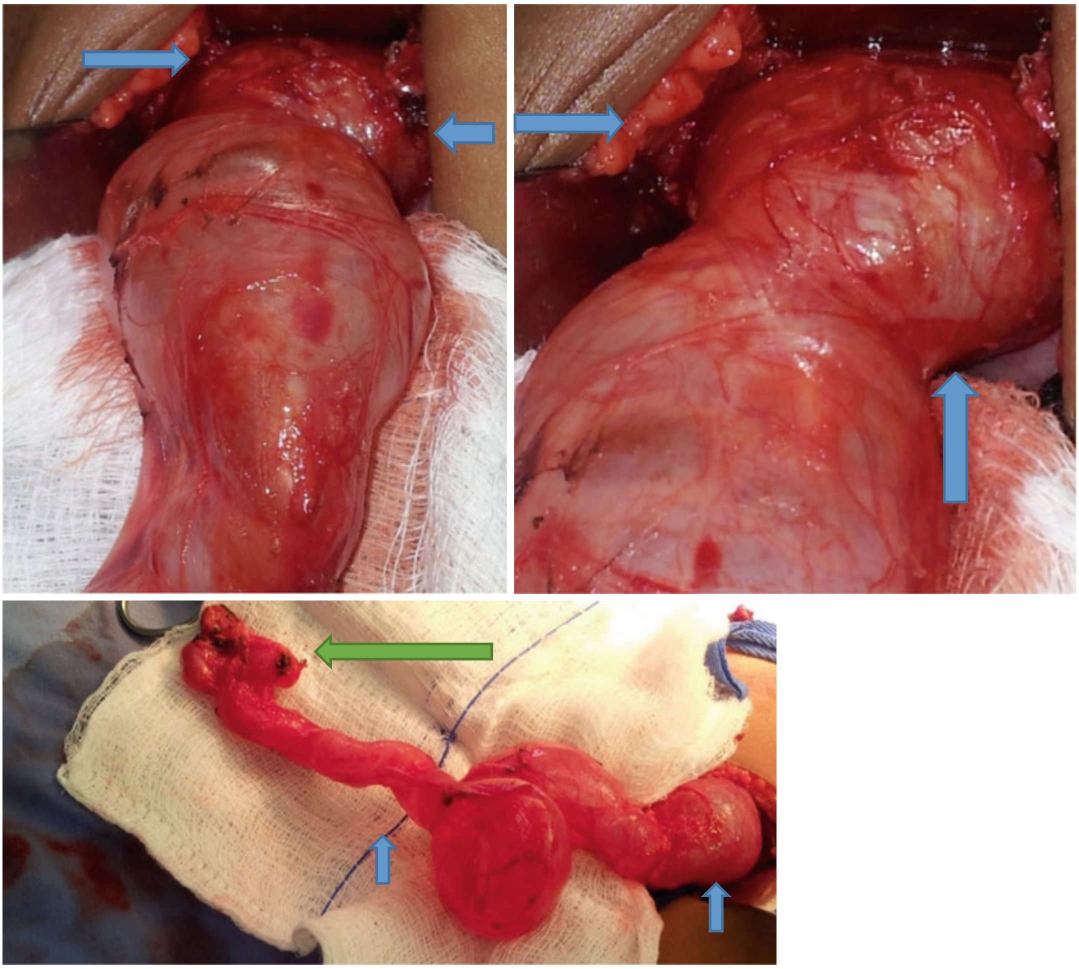
- A Dimercaptosuccinic acid (DMSA) radionucleotide scan:
  - This is useful to confirm poor function in the upper pole and also provides a baseline function prior to surgery.
- CT urography and Magnetic resonance urography (MRU):
  - These can define the anatomy more clearly including the site of the ureterocele, ureter and associated renal pathology (Figs. 6.28 and 6.29).
- Cystoscopy:
  - Cystoscopy is valuable to diagnose ureterocele.
  - It is useful to distinguish intravesical from ectopic ureteroceles.
  - When performing cystoscopy care must be taken not to obliterate the ureterocele; ideally the patient should be well hydrated, and irrigation flow kept to a minimum.

6.6.5 Treatment

- There are several treatment options that can be offered to a patient with a ureterocele (Figs. 6.30, 6.31, and 6.32).
- The treatment options include:
  - Conservative treatment
  - Ureterocele puncture
  - Upper pole hemi-nephrectomy
  - Ureterocele excision with bladder neck repair and re-implantation
- Ureterocele puncture is appropriate for emergency decompression of acutely infected systems and for intravesical ureteroceles.
- Upper pole hemi-nephrectomy carries a good success rate where there is no associated reflux.



Figs. 6.28 and 6.29 CT urography showing ureterocele. Note the associated dilated ureter



Figs. 6.30, 6.31, and 6.32 Clinical intraoperative photographs showing a very large ureterocele causing obstruction. Note the associated dilated ureter and the small atrophic dysplastic kidney

- Conservative treatment:
  - Expectant conservative treatment of antenatally detected ureteroceles may be successful.
  - This approach avoid potentially difficult surgery and its complications.
  - Leaving dysplastic renal tissue in situ may not pose an increased risk of hypertension.
  - The main concern over expectant management of ureteroceles is the predisposition of an obstructed hydronephrotic kidney to infection.
- Upper pole hemi-nephrectomy:
  - The upper pole of the kidney associated with a significant ureterocele usually has minimal function.
  - Upper pole hemi-nephrectomy will eliminate an obstructed system predisposed to urinary tract infection and suction of the distal ureter at the time will lead to collapse and decompression of the ureterocele.
  - Co-existing VUR to the lower pole is then expected to resolve in the majority of patients.
  - One important advantage of hemi-nephrectomy is that difficult surgery at the bladder neck and distal ureter is avoided.
  - With this approach, re-operation is avoided in 85 % of patients.
  - Bladder dysfunction seen in some of these patients is probably an inherent problem

  associated with ureterocele and not related to hemi-nephrectomy.
  - Heminephrectomy may be complicated by incontinence, UTI, diverticula and even bladder outlet obstruction.
- Ureterocele puncture/endoscopic treatment:
  - Endoscopic treatment of ureteroceles by puncture using cystoscopy is an alternative approach with much lower perioperative morbidity.
  - It can almost be performed as day-case surgery.
  - Endoscopic puncture provide emergency relief of obstruction in a child presenting with acute infection.
  - Endoscopic puncture has a high success rate for intravesical ureteroceles, and for these patients endoscopic puncture can be offered as a definitive treatment.
  - This however is not the case for those with ectopic ureteroceles where a high rate of re-operation should be expected. In these patients, endoscopic ureterocele puncture should be considered as part of a staged procedure. Endoscopic puncture in these patients makes subsequent reconstructive surgery easier, or enable VUR to be controlled endoscopically.
  - This puncture may need to be repeated in 10–20 % of patients.
  - Ureterocele puncture may be followed by recovery of some upper pole function.
  - Recovery of upper pole function is likely to be limited if underlying poor function is because of dysplasia rather than obstruction.
  - The main criticism of ureterocele puncture as a treatment modality is the need for further surgery, despite adequate decompression.
  - It was reported that about 47 % of patients with ureterocele treated by endoscopic puncture required further surgery. The risk of reoperation increases up to 70 % with extended follow-up.
  - The chance of re-operation is higher:
    - When the ureterocele is ectopic compared to intravesical
    - In a duplex system compared to a single system
    - If there is pre-existing reflux
  - The most common indication for re-operation is VUR.
  - This can affect half the patients having a ureterocele puncture and commonly affects the upper pole in about a third.
  - Treatment of VUR following ureterocele puncture is reimplantation.
  - Cystoscopic injection therapy has a success rate of 60–70 %.
- Bladder neck reconstruction:
  - The aim of bladder neck reconstruction is to correct the associated anatomical abnormalities.
  - Reconstruction may be performed as either the primary or secondary treatment.
  - Reconstruction surgery is difficult, especially when performed on a young infant.
  - In early life, ureterocele puncture may be performed to control the risk of UTI.
  - Reconstruction can then be performed at an older age when reconstruction surgery is easier.
  - Alternatively reconstruction has been performed as a primary procedure with good effect.
  - Reconstruction may include all or part of the following:
    - Excision of the ureterocele
    - Repairing the weakness of the bladder neck and bladder wall
    - Re-implantation of the associated ureters
    - Hemi-nephrectomy of a poorly functioning upper pole.
    - Marsupialization of the ureterocele, rather than its complete excision, may be performed to avoid difficult dissection in the urethra.
    - The benefit of reconstruction is that the functional problems associated with the ureterocele can all be corrected. These include:
      - VUR
      - Sphincter weakness
      - Bladder outlet obstruction
  - Uretero-ureterostomy:
    - This is a simple technique to treat children with ureterocele.
    - Uretero-ureterostomy has less morbidity when compared to heminephrectomy and or reconstruction.

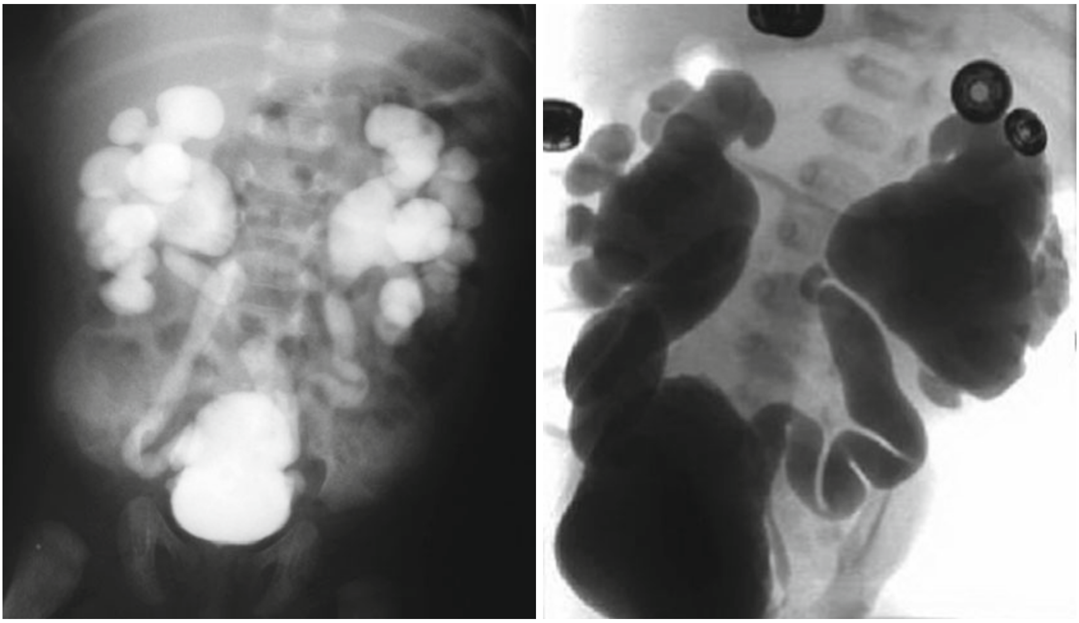
    - The procedure is based on anastomosing the upper pole ureter to the lower pole to provide effective drainage.
    - Uretero-ureterostomy may be combined with ureteric re-implantation of the less dilated ureter with good outcome.
    - One of the advantages of uretero-ureterostomy is that it can be performed through a small incision or laparoscopically.
- Single system ureterocele:
  - A fifth of all ureteroceles occur in single systems.
  - Single system ureteroceles are most commonly intravesical.
  - The associated kidneys often have reasonable function.
  - The majority of single system ureteroceles presenting in childhood are detected antenatally.
  - The treatment of single system ureterocele depends on the presence or absence of obstruction.
  - Conservative treatment:
    - If there is no obstruction or reflux of the affected kidney then non-surgical conservative treatment is appropriate.
  - Surgical treatment:
    - If the ureterocele impairs the drainage of an affected kidney then surgery is indicated.
    - Transurethral endoscopic puncture or incision of the ureterocele is much more likely to be successful in simplex system ureteroceles than in duplex kidneys.
    - Re-operation rates for ureteroceles in single systems are low (0–25 %).

6.6.5.1 Surgical Interventions

- Treatment of the ureterocele is based upon relief of obstruction.
- Endoscopic puncture may be used in cases in which urgent decompression is required (e.g. urosepsis, severe compromise in renal function), or it may be used as definitive therapy in the case of a single-system intravesical ureterocele.
- These include:
  - Urosepsis
  - Severe compromise in renal function.
- Endoscopic decompression in cases of ectopic ureterocele constitutes definitive treatment in only 10–40 % as there is frequently associated VUR, which often requires subsequent surgical correction.
- Options for open surgical reconstruction include ureteropyelostomy, ureteroureterostomy, excision of ureterocele and ureteral reimplantation, or upper-pole heminephrectomy with partial ureterectomy and ureterocele decompression.
- In patients with a single-system ureterocele and an associated nonfunctioning kidney, a nephroureterectomy may be performed.
- In the case of obstructive ureteroceles, treatment to relieve obstruction optimizes preservation of renal function as chronic obstruction can lead to renal deterioration.

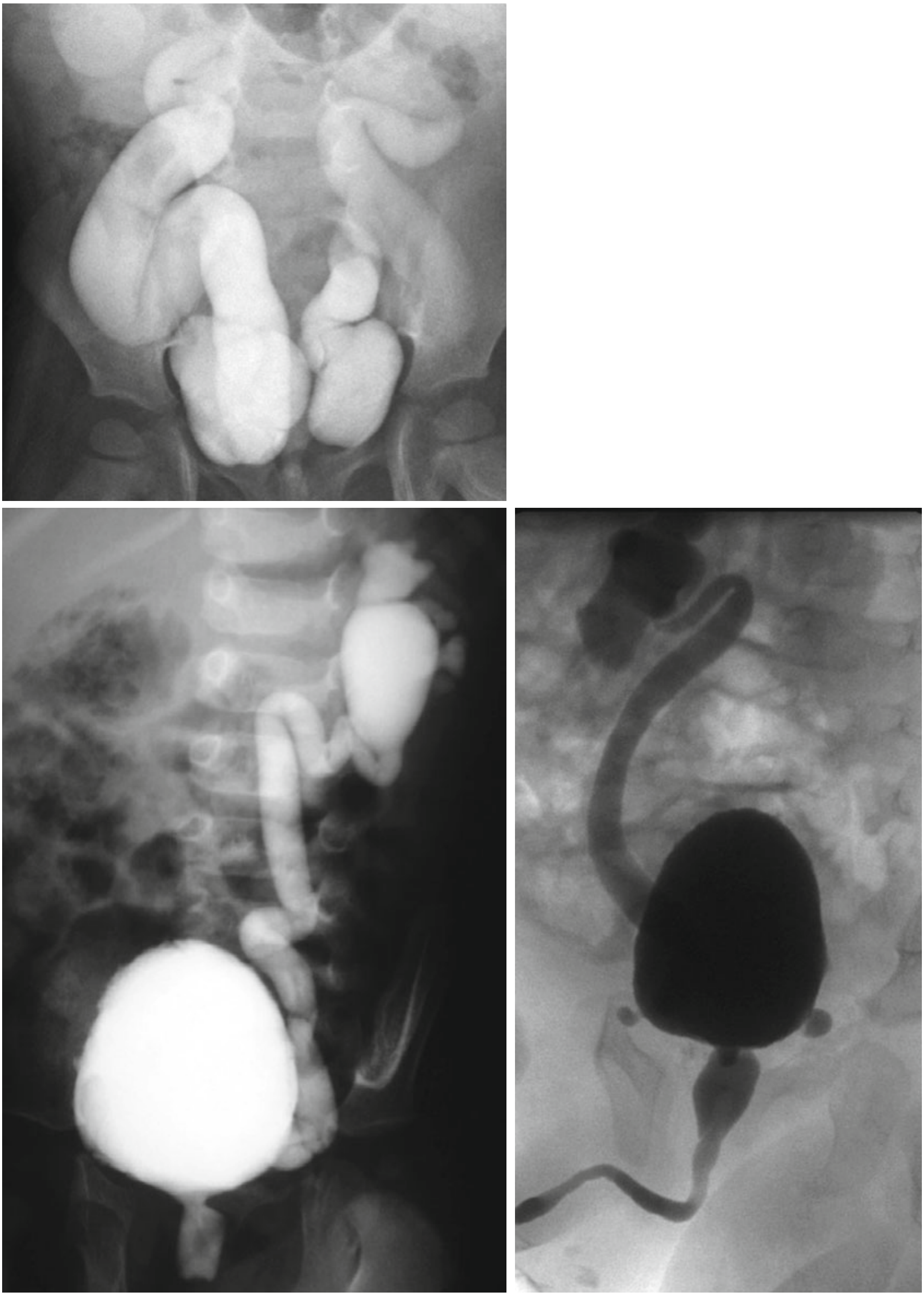
6.7 Vesicoureteral Reflux (VUR)

- VUR is retrograde flow of urine from the urinary bladder into the ureter and/or kidney (Figs. 6.33 and 6.34).
- One of the common complications of VUR is urinary tract infection.
- This causes reflux-induced renal injury.
- Reflux that is secondary to high bladder pressures such as those occurring in patients with posterior urethral valves (PUV) or bladder outlet obstruction is frequently associated with renal injury.
- Reflux-induced renal injury may range from clinically silent focal scars to generalized scarring and renal atrophy (reflux nephropathy).
- This may lead to:
  - Hypertension (renin-mediated)
  - Renal insufficiency
  - End-stage renal disease
- VUR may be associated with areas of renal dysplasia or hypoplasia.
- These are seen in the absence of urinary tract infection and may be due to abnormal renal development.

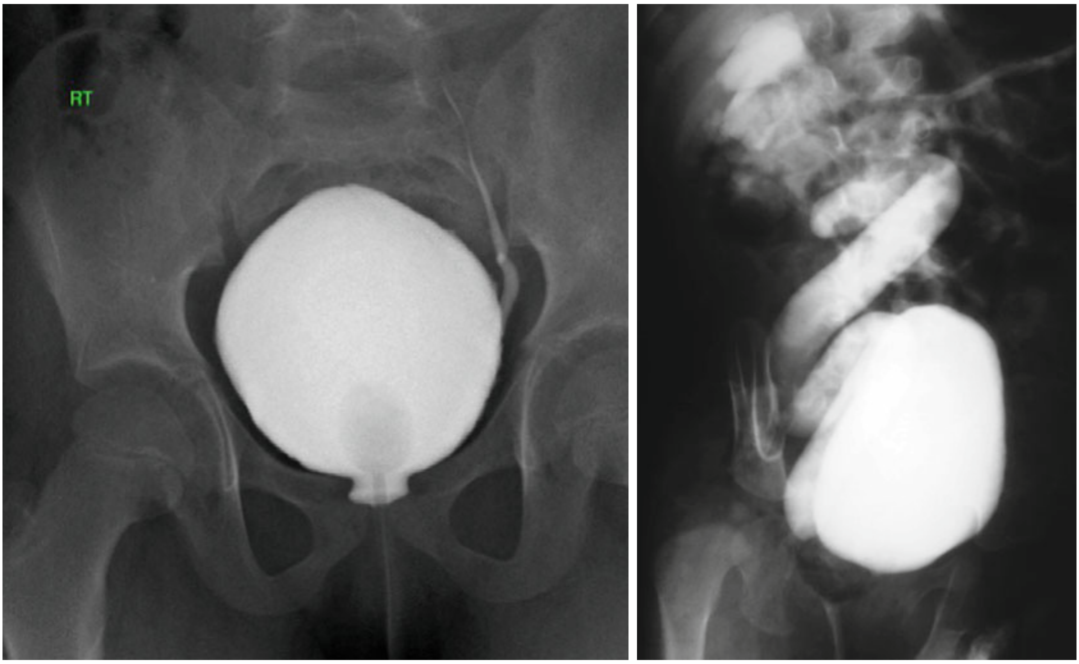


Figs. 6.33 and 6.34 Micturating cystourethrograms showing severe bilateral reflux

- The incidence of VUR in otherwise healthy children is approximately 1 %.
- The incidence is approximately 40 % in patients undergoing evaluation for UTI.
- The reported risk of reflux in a sibling is 27–43 %.
- Approximately 50 % of the offspring of women with reflux will also have VUR.
- Normally, the distal ureter enters the urinary bladder through a submucosal tunnel.
- The submucosal tunnel length is the most important component of a competent uretrovesical junction.
- A competent uretrovesical junction provides a one way valve that allows antegrade passage of urine from the ureter into the urinary bladder.
- This one way valve prevents retrograde passage of urine from the urinary bladder into the ureter.
- Failure of this uretrovesical junction one way valve will result in VUR.
- Vesicoureteral reflux is divided into two types based on etiology.
- Primary VUR:
  - This is secondary to a congenitally deficient UVJ
- Secondary VUR:
  - This is secondary to several factors that affect the uretrovesical junction.
  - These factors include (Figs. 6.35, 6.36, and 6.37):
    - Loss of UVJ compliance during UTI
    - Bladder diverticulum
    - Ureterocele
    - Neurovesical dysfunction or neurogenic bladder
    - Bladder outlet obstruction
- Indications for surgical interventions:
  - Absolute indications:
    - Progressive renal injury
    - Documented failure of renal growth
    - Breakthrough pyelonephritis
    - Intolerance or noncompliance with antibiotic suppression
    - Parental preference
  - Relative indications:
    - Pubertal age
    - High-grade (IV or V) VUR (Figs. 6.38 and 6.39)
    - Failure to resolve
- Increasing experience shows that a considerable number of children with VUR may



Figs. 6.35, 6.36, and 6.37 Micturating cystourethrograms showing primary VUR and secondary VUR associated with posterior urethral valves



Figs. 6.38 and 6.39 Micturating cystourethrograms showing mild and severe VUR

demonstrate improved renal function on radiography, without surgical intervention.

- Nonoperative treatment mandates close follow-up care in patients with VUR.
- Nonoperative management of VUR includes:
  - Antimicrobial suppression
  - Treatment of voiding dysfunction
  - Regular imaging studies to assess renal growth, renal scarring, and possible resolution of pathology.
- The need for antibiotic prophylaxis in all patients with VUR has been brought into question.
- Current recommendations include low-dose antibiotic suppression in children younger than 1 year with VUR and a history of febrile UTI, based on greater morbidity from recurrent UTI in this population.
- Use of antibiotic prophylaxis in older children with VUR should be made on an individualized basis; however, the use of prophylaxis would appear to be the most beneficial in those with grade 3 or greater reflux, girls, those with a significant history of recurrent febrile UTIs, and/or those with bowel or bladder dysfunction.
- Surgical treatment:
  - Because the submucosal ureter tends to lengthen with age, the ratio of tunnel length to ureteral diameter also increases, and the propensity for reflux may disappear.
  - Successful nonoperative management of VUR requires preventing renal damage from pyelonephritis and has involved the use of continuous antibiotic prophylaxis and treating bowel or bladder dysfunction.
  - Dextranomer hyaluronic acid copolymer is a bulking agent for endoscopic treatment of VUR.
  - Endoscopic treatment results in reflux resolution or downgrading in most patients, with long-term success rates of approximately 60–70 %.
  - Although not as effective as open ureteral reimplantation, endoscopic correction of VUR offers a minimally invasive, outpatient procedure with a low risk of complications.
  - In general, ureteral reimplantation has excellent results (>95 % success rate). Although the transvesical approach is

  commonly used, the extravesical approach (detrusorrhaphy) preserves the integrity of the bladder lumen and does not require a ureteral anastomosis. Extravesical reimplantation has been shown to decrease postoperative hematuria, minimize bladder spasms, reduce the need for urethral catheter, and shorten hospital stay. Of note, transient cases of urinary retention have been reported with bilateral extravesical ureteral reimplant. Although open ureteral reimplantation remains the gold standard, minimally invasive techniques (robotic assisted ureteral reimplantation) have demonstrated comparable success rates.

- Complications of ureteral reimplantation are uncommon.
- The most common technical complications are ureteral obstruction, persistent reflux, and diverticula formation.
- Ureteral reimplantation for mega ureter repair is a very safe, reproducible, and successful procedure.
- The major complications are the development of ureteral obstruction (2–5 %) or VUR (approximately 10 %).
- Ureteral obstruction is most likely the result of ureteral ischemia and subsequent fibrosis of an excisionally tapered segment.
- Initial management of this complication is percutaneous or endoscopic dilatation and stenting of the stricture, but many such instances ultimately require open surgical revision.
- If postoperative VUR is encountered, a reasonable treatment option is observation and antibiotic prophylaxis because many reflux cases resolve spontaneously.
- In addition, VUR is more likely to recur following reimplantation in cases in which bladder pressures are elevated (e.g. patients with untreated neuropathic bladders or voiding dysfunction).
- Treatment of bladder/bowel dysfunction is indicated, preferably prior to surgical intervention of VUR. Careful assessment of voiding symptoms and a low threshold for urodynamic studies are crucial in the evaluation of patients with recurrent VUR.
- Cases of high-grade VUR are less likely to spontaneously resolve and more likely to put the kidney at risk of scarring due to pyelonephritis.
- Prevention of infection is essential to minimize the risk of renal damage; therefore, continuous antibiotic prophylaxis is usually used in children with high-grade VUR while awaiting spontaneous resolution.
- Robotic-assisted ureteral reimplantation has gained popularity and will continue to evolve with time, although open ureteral reimplantation currently remains the criterion standard for surgical management of VUR.
- Antibiotic prophylaxis for all children with VUR remains controversial, although it is recommended in children younger than 1 year with a history of febrile UTI or grade III reflux or higher.
- Bowel and bladder dysfunction are often associated with VUR and increase the risk of pyelonephritis, so should be evaluated and treated aggressively in children with VUR.

6.8 Mega Ureter

- The term mega ureter refers to an enlarged ureter.
- A mega ureter is a wide ureter, greater than 7 mm in diameter (Fig. 6.40).
- Light microscopy of mega ureters demonstrates a predominance of circular smooth muscle; muscle fiber hypoplasia and atrophy, with collagen deposits separating the muscle cells; and mural fibrosis with scant muscle fibers.
- Electron microscopy of mega ureters demonstrates increased collagen deposition within the adynamic segment.
- Megaureters may be classified into the following four categories:
  - Obstructed
  - Refluxing
  - Obstructed and refluxing
  - Nonobstructed/nonrefluxing
- Each of these categories is further divided into:
  - Primary
  - Secondary

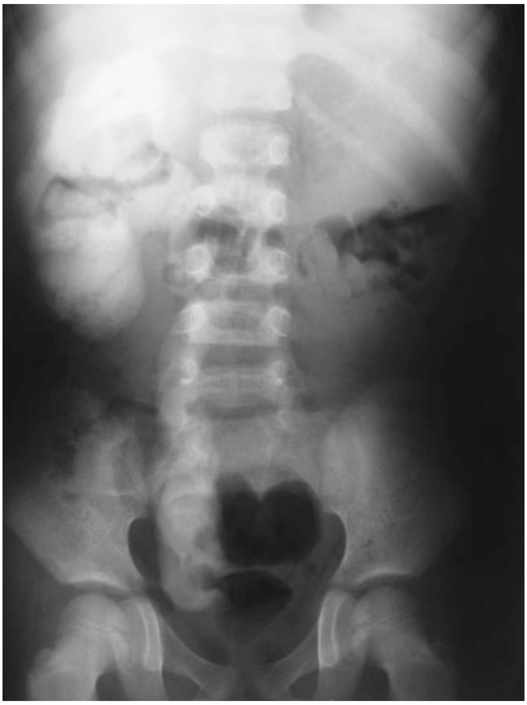


Fig. 6.40 Intravenous urography showing a right mega ureter secondary to uretero-vesical junction obstruction

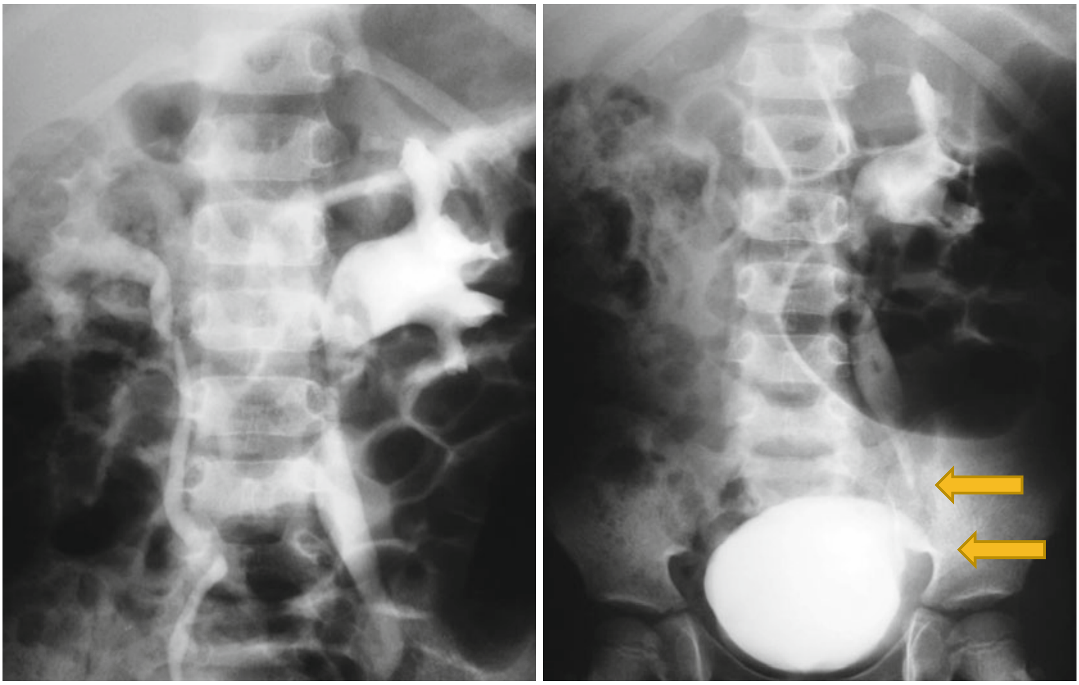
Classification of Mega Ureter

- Primary
- Secondary

Mega ureters are also classified into:

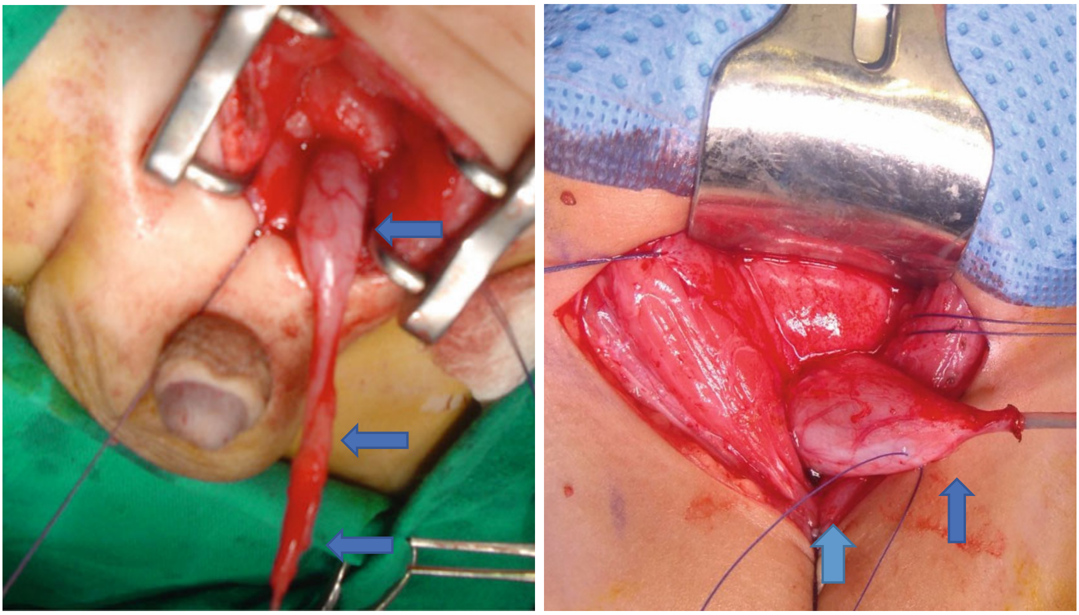
- Obstructive
- Reflexing
- Obstructed and refluxing
- Nonobstructed/Nonrefluxing

- This is based on their etiology, either intrinsic or extrinsic.
- Bilateral involvement is present in about 20 % of patients with primary obstructed mega ureters.
- Primary obstructed mega ureter has a male-to-female ratio of nearly 4:1.
- The left side is more often affected than the right.
- Primary obstructed mega ureter:
  - This is most commonly caused by an adynamic juxtavesical segment of the ureter that fails to effectively propagate urine flow (Figs. 5.41 and 5.42).
- Secondary obstructed mega ureter:
  - This occurs usually when ureteral dilatation is the result of a functional ureteral obstruction associated with elevated bladder pressures secondary to PUV or a neurogenic bladder that impedes ureteral emptying.
- Primary refluxing mega ureter:
  - This is associated with severe VUR that alters ureteral efficiency by ureteral distention.
  - The megaureter-megacystis syndrome is an extreme form of the primary refluxing mega ureters in which massive reflux prevents effective bladder emptying because urine is passed back and forth between the ureters and bladder.
- Secondary refluxing mega ureter:
  - This occurs secondary to PUV or neurogenic bladder when elevated bladder pressures cause decompensation of the uretrovesical junction.
- Primary nonrefluxing/nonobstructed mega ureter:
  - This is diagnosed when no evidence of obstruction or reflux can be demonstrated.
- Secondary nonrefluxing/nonobstructed mega ureter:
  - This occurs secondary to diabetes insipidus, in which high urinary flow rates may overwhelm the maximum transport capacity of the ureter by peristalsis or as the result of ureteral atony accompanying a gram-negative UTI.
- Primary refluxing obstructed mega ureter:
  - This occurs in the presence of an incompetent VUJ that allows reflux through an adynamic distal segment.
- Indications for surgical interventions:
  - Increasing hydroureteronephrosis
  - Decrease in renal function of involved kidney
  - Development of UTI or recurrent pain
- Increasing experience shows that a considerable number of children with mega ureters without reflux or obstruction may demonstrate improved renal function on radiography, without surgical intervention.

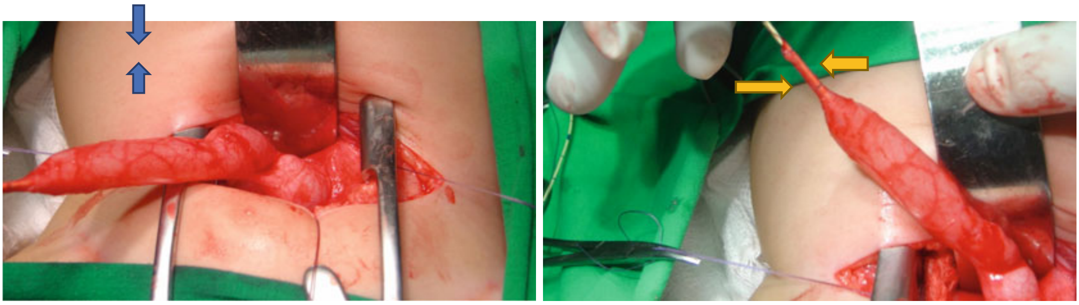


Figs. 6.41 and 6.42 Intravenous urography showing megaureter. Note the small caliber of the distal ureter

- Nonoperative treatment mandates close follow-up care in patients with nonobstructed/nonrefluxing mega ureters.
- Nonoperative management of nonobstructed primary mega ureter includes antimicrobial suppression, treatment of voiding dysfunction, and regular imaging studies to assess renal growth, renal scarring, and possible resolution of pathology.
- Mega ureter secondary to severe VUR or obstruction is usually managed with ureteral reimplantation (Figs. 6.43, 6.44, 6.45, and 6.46).
- Reimplantation techniques are similar to those used for correcting primary VUR.
- The mega ureter can be mobilized via an intravesical, extravesical, or combined approach.
- Most mega ureters will require tapering.
- The ureteral caliber can be reduced by excising the distal redundant ureter (Hendren technique) or plication (Kalicinski technique, Starr technique) to achieve a satisfactory antireflux mechanism.
- Occasionally, the function of the kidney drained by a mega ureter is severely impaired, and nephroureterectomy may be necessary.
- There have been reports of obstructive mega ureters treated successfully by endoscopic dilation.
- Complications of ureteral reimplantation are uncommon.
- The most common technical complications are ureteral obstruction, persistent reflux, and diverticula formation.
- Ureteral reimplantation for mega ureter repair is a very safe, reproducible, and successful procedure.
- The major complications are:
  - The development of ureteral obstruction (2–5 %)
  - VUR (approximately 10 %).
- Ureteral obstruction is most likely the result of ureteral ischemia and subsequent fibrosis of an excisionally tapered segment.
- With respect to primary mega ureters, as in the case of VUR, spontaneous resolution is common.
- In the case of the obstructed primary mega ureter, spontaneous resolution is less likely to occur; however, a study reported a 70 % spontaneous regression.



Figs. 6.43 and 6.44 Clinical intraoperative photographs showing megaureters secondary to a stenosed adynamic lower ureteric segment. Note the diameter of the stenosed segment of the lower ureter. Note also the dilated ureter proximal to the stenotic segment



Figs. 6.45 and 6.46 Clinical intraoperative photographs showing megaureters secondary to a stenosed adynamic lower ureteric segment. Note the diameter of the stenosed segment of the lower ureter. Note also the dilated ureter proximal to the stenotic segment

Further Reading

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Congenital Megaureter

7

7.1 Introduction

- The term megaureter refers to an enlarged dilated ureter (Fig. 7.1).
- In children, any ureter greater than 7 mm in diameter is considered a megaureter.
- The megaureter is divided into two main groups depending on etiology:
  - Primary megaureter:
    - This results from a functional or anatomical abnormality involving the ureterovesical junction (Fig. 7.2).
  - Secondary megaureter:
    - This results from abnormalities that involve the bladder or urethra including:
      - Myelomeningocele/neurogenic bladder
      - Severe urethral stricture
      - Posterior urethral valves
- Primary megaureter is further sub classified according to the presence or absence of reflux and obstruction.
- Megaureter is divided into four types:
  - Refluxing megaureter
  - Obstructed megaureter
  - Refluxing/obstructed megaureter
  - Non-refluxing/ non-obstructed megureter
- Each of these types is further subdivided into primary or secondary:
  - This is based on either intrinsic or extrinsic causes for their appearance.
- Bilateral involvement is present in about 20% of patients with primary obstructed megaureter.
- The left side is more commonly affected than the right (1.6–4.5 times).
- Primary obstructed megaureter is more common in males with male-to-female ration of about 4:1.
- Congenital primary megaureter is an idiopathic condition in which the bladder and bladder outlet are normal but the ureter is dilated.

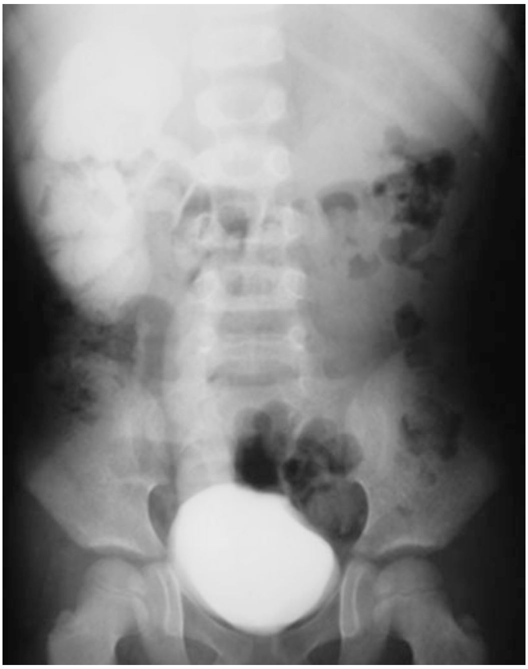

Fig. 7.1 Intravenous urography showing a right megaureter. Note the markedly dilated ureter causing back pressure on the kidney

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A.H. Al-Salem, *An Illustrated Guide to Pediatric Urology*, DOI 10.1007/978-3-319-44182-5_7

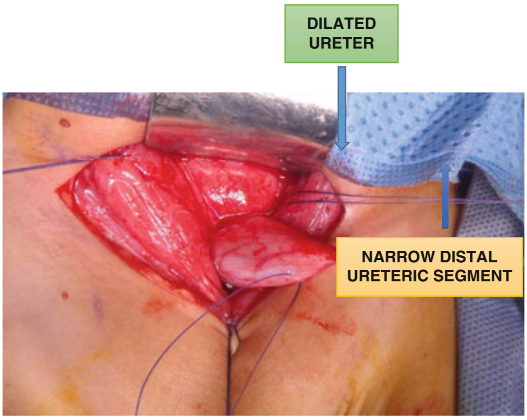
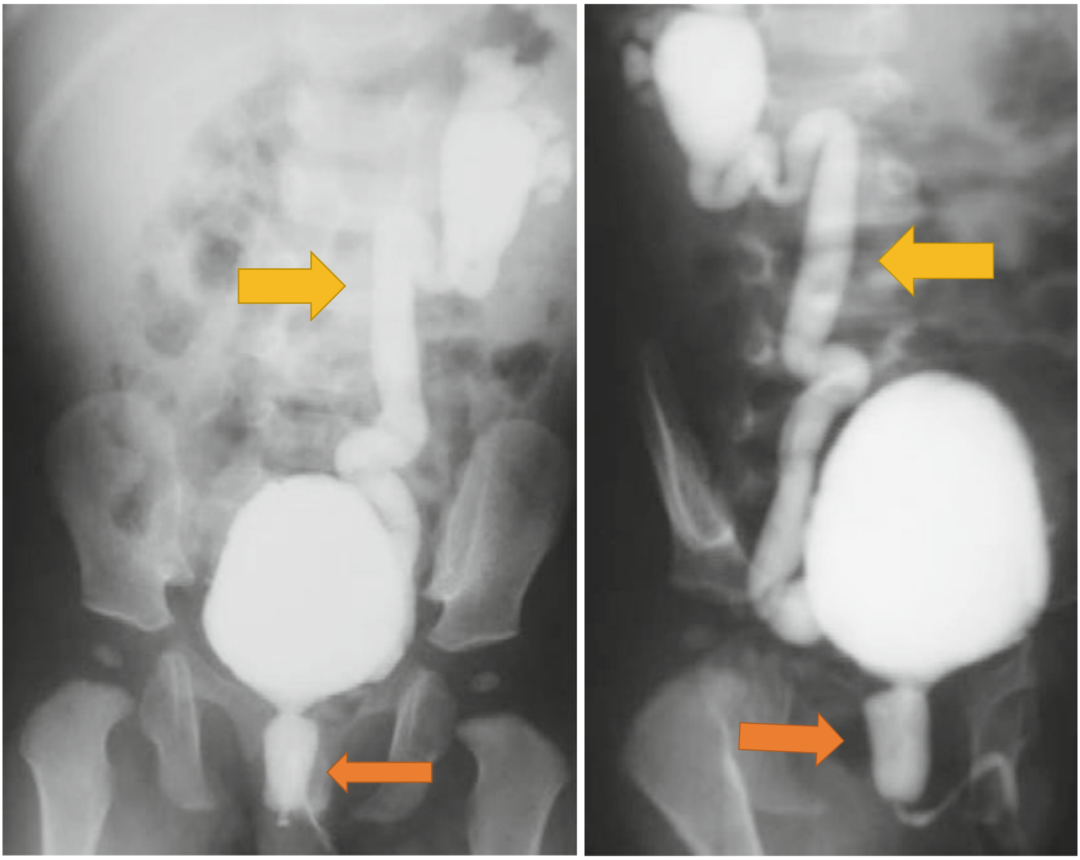


Fig. 7.2 A clinical intraoperative photograph showing a primary megaureter. Note the small narrowed distal ureteric segment which is aperistalitic

- Primary megaureter is the second most common cause of neonatal hydronephrosis.
- The majority of cases are non-refluxing and unobstructed.
- The incidence of obstructed megaureter is 1 in 10,000 live newborns.
- Most primary megaureter in neonates is non-refluxing and unobstructed.
  - The etiology of this is unknown
  - It may be due to high fetal urine outflow
  - It may be caused by changes in the ureter pre- and postnatal or transient anatomical obstructions that improve with postnatal development, such as ureteral folds.
- In unilateral primary megaureter the contralateral kidney is absent or dysplastic in 10–15 % of patients.
- About 50 % of primary megaureter cases are asymptomatic and are discovered on routine antenatal ultrasound.
- Most asymptomatic patients have unobstructed primary megaureter.
- Symptomatic primary megaureter present with:
  - Urinary tract infections
  - Hydronephrosis
  - Fever
  - Abdominal and flank pain
  - Microscopic hematuria is frequent and may occur without infection.
  - The presence of microscopic hematuria may indicate calculus formation.
  - These patients rarely present with signs of renal failure.
- Vesicoureteric reflux disease (VUR): although actually a cause of primary congenital megaureter it is usually considered separately as prognosis and treatment, depending on degree of reflux, is different
- Causes of secondary megaureter include (Figs. 7.3, 7.4, 7.5, 7.6, 7.7, 7.8, 7.9, 7.10, 7.11, 7.12, 7.13, and 7.14):
  - Posterior urethral valve: This is often associated with bilateral hydroureter/hydronephrosis
  - Ureteral diverticulum
  - Urolithiasis
  - Urotrocele
  - Duplex collecting system with reflux into lower pole moiety
  - Myelomeningocele/neurogenic bladder
  - Severe urethral stricture
- Primary megaureter is a common cause of obstructive uropathy among neonates and young children.
- It is estimated that vesico-ureteric junction obstruction account for 23 % of neonates diagnosed with obstructive uropathy.
- Children presenting before 1 year old are more likely to have bilateral Primary megaureter than are older patients.
- The condition is not known to be hereditary, but families with more than one member with PM have been described.

7.2 Classification

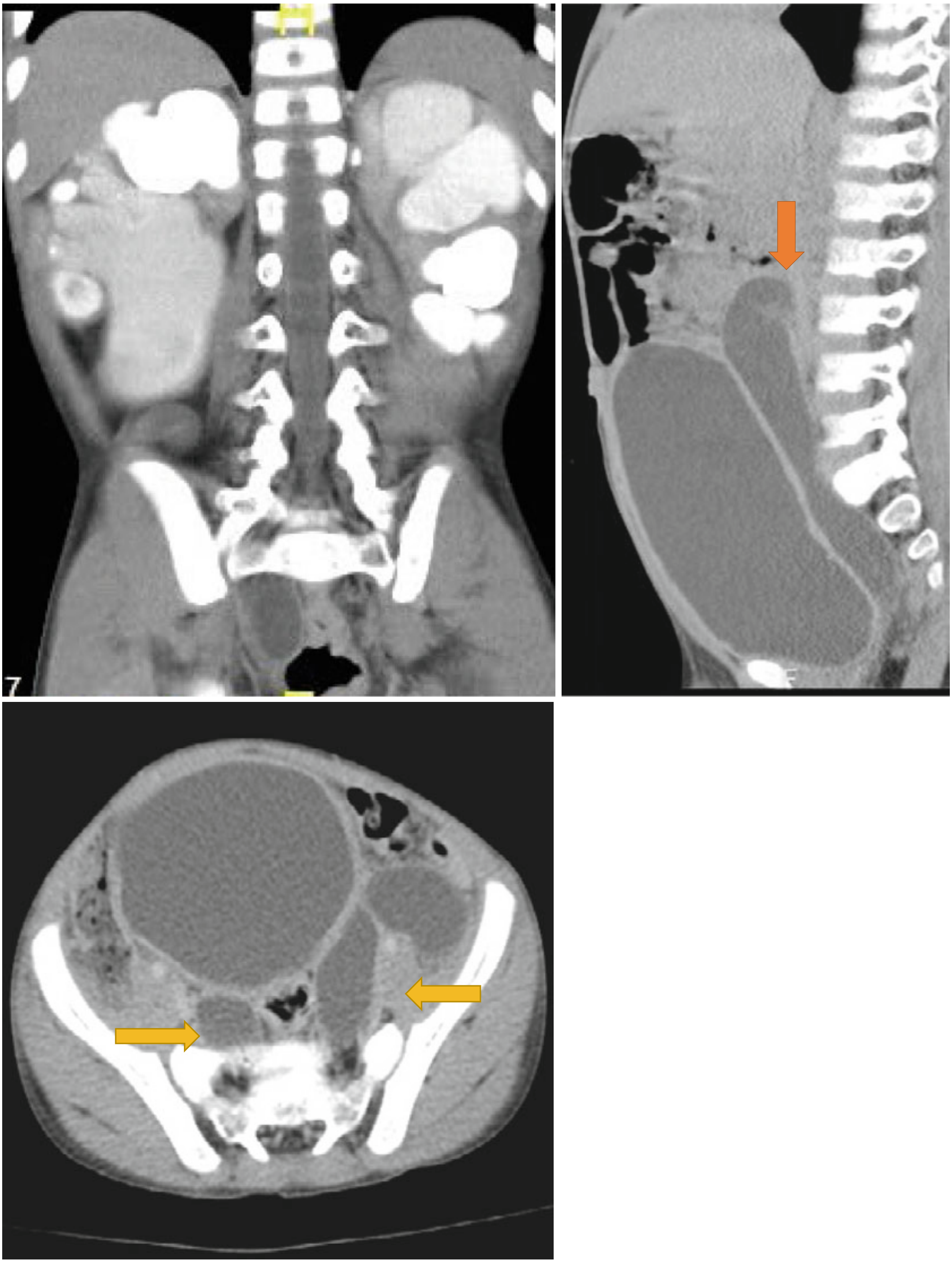
- The term ‘megaureter’ could be applied to any dilated (mega) ureter.
- In general use, the term megaureter is not applied to a hydroureter caused by overt



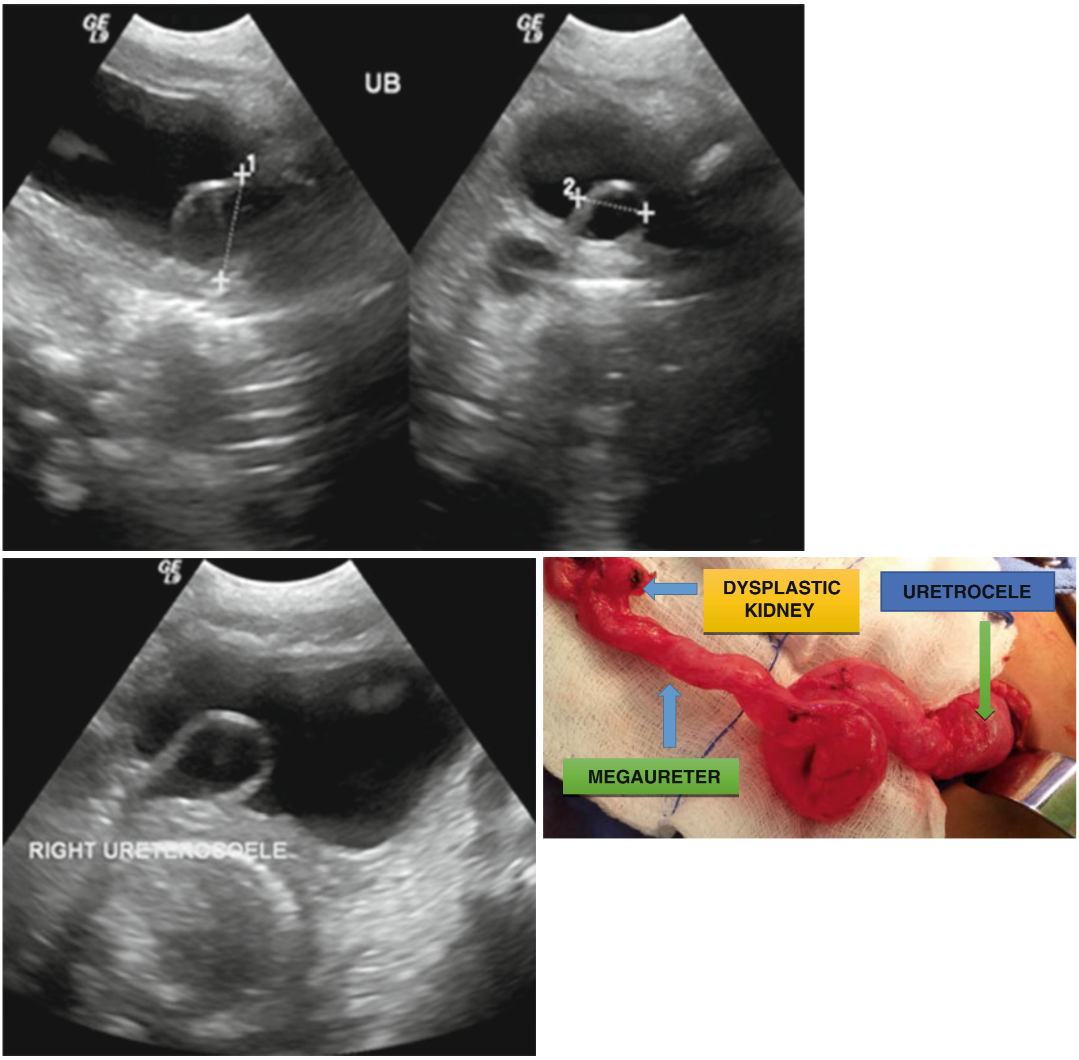
Figs. 7.3 and 7.4 Micturating cystourethrograms showing posterior urethral valves and associated vesicoureteral reflux

neuropathic bladder or typical bladder neck obstruction.

- Megaureter is usually reserved for conditions in which the bladder and bladder outlet are normal but the ureter is dilated.
- Many classifications were proposed for megaureter.
- The international classification of Smith et al. is the most comprehensive classification.
  - Obstructed
  - Refluxing
  - Unobstructed
  - None refluxing
- Each of these categories is subdivided into a primary and secondary group.
- In primary megaureter the cause is idiopathic.
- Secondary megaureter may be caused by:
  - Urethral obstruction
  - Bladder outlet obstruction
  - Neurogenic bladder
  - Polyuria
  - Infection
- A more practical classification of megaureter was given by King as:
  - Refluxing
  - Obstructed
  - Not refluxing
  - Not obstructed
  - Refluxing and obstructed



Figs. 7.5, 7.6, and 7.7 CT-urography showing duplex system and bilateral hydroureteronephrosis. Note the dilated megaureters



Figs. 7.8, 7.9, and 7.10 Pelvic ultrasound and intraoperative photograph showing uretrocele. Note the markedly dilated ureter

- Primary megaureter usually includes:
  - Obstructed primary megaureter
  - Unobstructed primary megaureter
- Secondary megaureter is caused by a variety of urological disorders.
- Primary obstructed megaureter:
  - This is most commonly caused by an adynamic juxtavesical segment of the ureter that fails to effectively propagate urine from the ureter into the urinary bladder.
- Secondary obstructed megaureter:
  - This occurs usually when ureteral dilatation is the result of a functional ureteral obstruction associated with elevated bladder pressures secondary to PUV or a neurogenic bladder that impedes ureteral emptying.

Classification of Megaureter

- The international classification of Smith et al. is the most comprehensive classification.
  - Obstructed
  - Refluxing
  - Unobstructed
  - None refluxing
- Each of these categories is subdivided into a primary and secondary group.
  - Primary obstructed megaureter
  - Secondary obstructed megaureter
  - Primary refluxing megaureter
  - Secondary refluxing megaureter
  - Primary nonrefluxing/nonobstructing megaureter
  - Secondary nonrefluxing/nonobstructing megaureter
  - Primary refluxing/obstructed megaureter

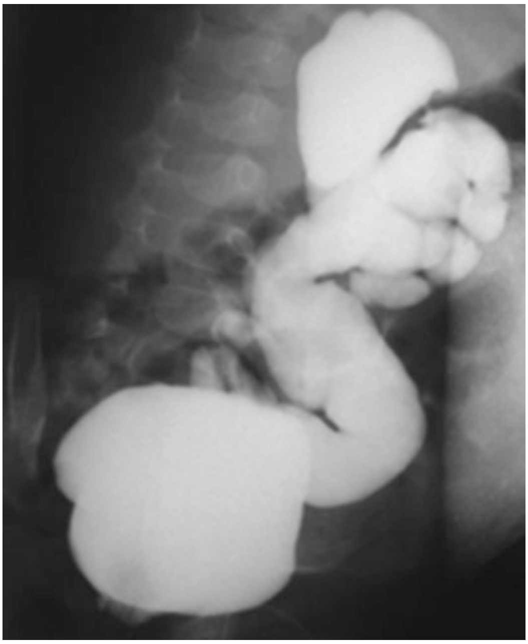


Fig. 7.11 Micturating cystourethrogram showing massively dilated ureter

- Primary refluxing megaureter:
  - This is associated with severe VUR that alters the uretero-vesical junction leading to dilatation of the ureter.
  - The megaureter-megacystis syndrome is an extreme form of primary refluxing megaureters.
- Secondary refluxing megaureter:
  - This occurs secondary to posterior urethral valve and neurogenic bladder.
  - Elevated urinary bladder pressure causes decompensation of the one-way valve at the uretero-vesical junction.

Class	Primary	Secondary
Obstructed	Intrinsic ureteric obstruction (an adynamic juxtavesical segment of the ureter)	Infravesical obstruction (elevated bladder pressure secondary to PUV or a neurogenic bladder that impedes ureteral emptying)
Refluxing	Reflux is the only abnormality (severe VUR that alters the uretero-vesical junction)	Associated with bladder outlet obstruction or neurogenic bladder (Elevated urinary bladder pressure causes decompensation of the uretero-vesical junction
Non-refluxing/ unobstructed	Idiopathic ureteric dilatation (No obstruction or reflux)	Polyuria (diabetes insipidus) or gram – ve UTI

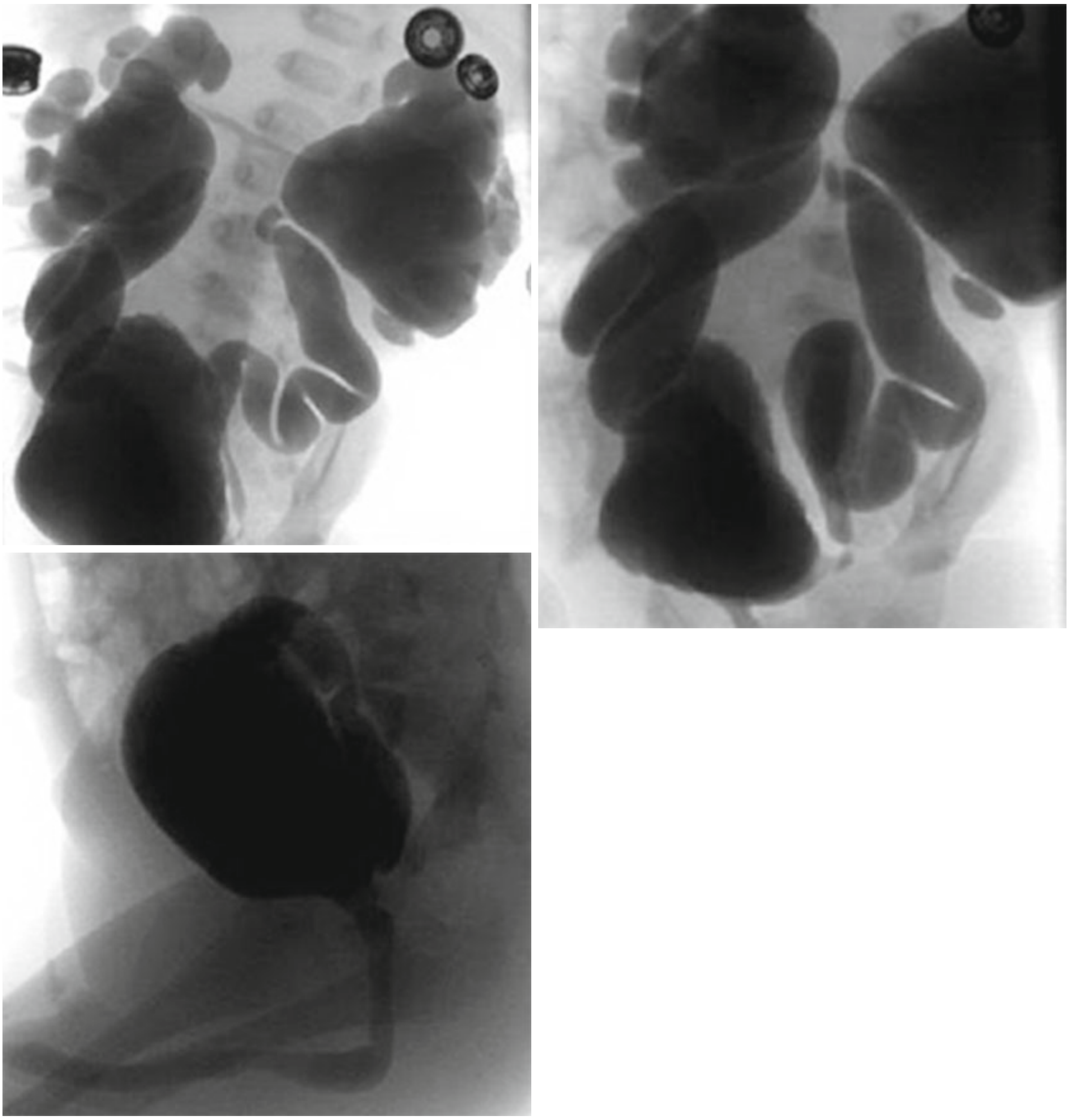
- Primary nonrefluxing/nonobstructed megaureter:
  - This is diagnosed when no evidence of obstruction or reflux can be demonstrated.
- Secondary nonrefluxing/nonobstructed megaureter:
  - This occurs secondary to diabetes insipidus, in which high urinary flow rates may overwhelm the maximum transport

  capacity of the ureter by peristalsis or as the result of ureteral atony that accompany a gram-negative urinary tract infection.

- Primary refluxing obstructed megureter:
  - This occurs in the presence of an incompetent VUJ that allows reflux through an adynamic distal segment.

7.3 Etiology and Pathophysiology

- Primary obstructive megaureter:
  - It is a common cause of obstructive uropathy in children.
  - There is a general agreement that there is no true narrowing at the VUJ.



Figs. 7.12, 7.13, and 7.14 Micturating cystourethrogram showing severe bilateral reflux and megaureters. Note the absence of posterior urethral valve

- This is a functional obstruction secondary to a distal adynamic juxtavesical segment 0.5–4 cm long that is unable to transport urine at acceptable rates.
- This leads to proximal ureteric dilatation.
- The exact etiology of this aperistatic segment is not known.
- Several etiological theories have been proposed including:
    - Excessive collagen deposition.
    - Increased matrix deposition alters cell-to-cell junctions and disrupts myoelectrical propagation and peristalsis.
    - Segmental changes of ureter muscle cells, where there is atrophy of the inner longitudinal layer that conducts the peristaltic waves and hypertrophy of the outer circular layer that causes obstruction.
    - Thick circumferential periureteral tissues devoid of muscle.
    - A bulky peri-ureteric sheath
    - A thick sleeve of muscle forming a continuous layer surrounding the muscle bundles of the terminal ureter. The muscle forming this outer layer is distinct in its histological appearance and arrangement from the muscle bundles which form the ureteric muscle of the VUJ. Furthermore, this muscle layer is very densely innervated by nonadrenergic (immunoreactive to dopamine beta-hydroxylase) nerves when compared with the smooth muscle coat of the ureter. This dense nonadrenergic innervation of this muscle collar might cause it to constrict inappropriately, impeding urinary flow, and ultimately lead to the development of megaureter.
    - The altered peristalsis prevents the free outflow of urine and functional obstruction results.
- The fact that the distal ureter is the last portion of the ureter to develop its muscular coat and that early muscular differentiation is primarily of the circular muscle may explain why the aperistalitic segment affect only the distal segment of the ureter.
- This was supported by the finding of TGF-**β** in the aperistalitic segment but not in the dilated ureter and since TGF-**β** is not normally found in the ureter, a developmental abnormality may explain its pathogenesis.
- This also may explain the frequent spontaneous resolution of primary megaureter within the first 2 years of postnatal life, where the circular muscular pattern, which is typical of the fetal ureter, changes progressively into the double muscle layers of the full-term infant.
- The degree of ureteric dilatation that results depends on the amount of urine forced to accumulate proximally.
- This in turn is determined by the degree of distal obstruction and urinary output.
- The dilated ureter provide a larger reservoir and hence less likely to transmit damaging pressure to the kidney.

- Primary refluxing megaureter:
    - Primary refluxing megaureter results from an abnormal vesico-ureteric junction, which impedes the normal anti-reflux mechanisms.
    - This can be due to:
        - A short intravesical ureter
        - Congenital paraureteric diverticulum
        - Ureterocoele with or without associated duplicated collecting system
        - Other derangement of the vesico-ureteric junction
    - It may be associated with megacystis megaureter syndrome and prune belly syndrome.
    - The marked increase in collagen and significant decrease in smooth muscle could be a major contributing factor in the pathogenesis of refluxing primary megaureter.
    - There are a few patients with refluxing primary megaureter who have the megacystis-megaureter association, with the characteristics of:
        - Bilateral hydroureteronephrosis
        - A large thin-walled urinary bladder
        - Bilateral high-grade VUR
    - Another special group of patients with dilated ureters are those with prune-belly syndrome,

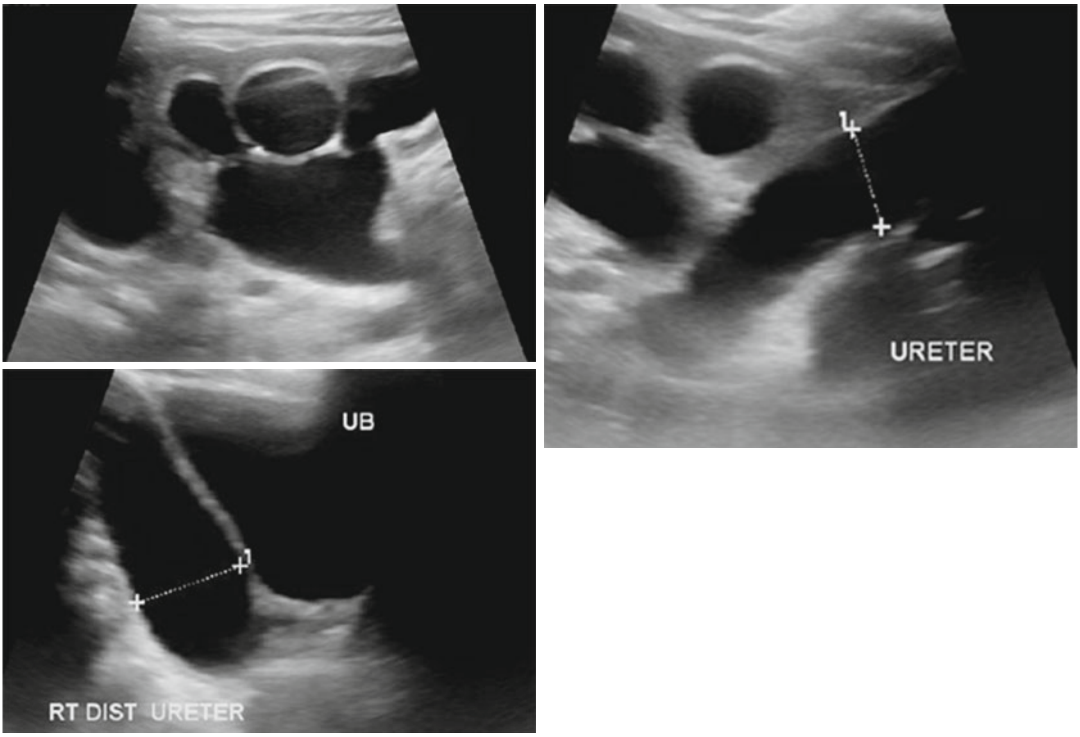
  in which the dilated ureters may be caused by reflux or VUJ obstruction, or maybe not refluxing and unobstructed, and categorized according to these characteristics.
  - A dysgenetic distal ureteric segment that not only fails to cope within the intramural tunnel but also has ineffective peristalsis is implicated in its pathogenesis.
- Non-refluxing unobstructed primary megaureter:
  - This is thought to be the most common cause of primary megaureter in neonates, and even though the vesicoureteric junction is normal, with no evidence of reflux or obstruction the ureter is enlarged.
  - Most primary megaureter in neonates fall into this category.
  - There is neither reflux nor stenosis of the juxtavesical ureter, but the ureter is dilated beginning at a point just above the bladder.
  - The cause of this phenomenon is unknown.
  - Several theories were proposed:
    - Fetal urine production is four to six times greater before than after delivery. This is because of differences in renal vascular resistance, GFR and concentrating ability.
    - This high outflow might contribute to ureteric dilatation in the absence of functionally significant obstruction, as is occasionally seen with diabetes insipidus.
    - Another contributing factor appears to be increased compliance of the fetal ureter because of differences in the deposition of type III collagen, elastin and other extracellular matrix proteins.
    - Partial or transient anatomical or functional obstructions that spontaneously improve with postnatal development could contribute to proximal ureteric dilatation.
    - Persistent fetal ureteric folds or delays in the development of normal ureteric peristalsis may be responsible for such transient obstructions.
- Primary megaureter is not known to be hereditary, but families with more than one affected member have been described.
- Primary megaureter may be associated with renal agenesis, megacalycosis and urolithiasis.

7.4 Clinical Presentation

- The widespread use of obstetrical US with concomitant fetal screening resulted in an increase in the prenatal diagnosis of congenital uropathies, including megaureter.
- Currently, about half of the cases of congenital megaureter are asymptomatic and discovered on prenatal US.
- Symptomatic patients commonly present with UTI, fever and abdominal pain.
- Microscopic hematuria is frequent and may occur in the absence of urinary tract infection. This is presumably caused by the disruption of mucosal vessels of the ureter secondary to ureteric distension.
- Hematuria may also be a sign of calculus formation secondary to urinary stasis.
- It is not unusual for the dilated asymptomatic ureter to be noted at the time of abdominal surgery for other reasons.
- Rarely, these patients present late with signs of renal failure.

7.5 Investigations and Diagnosis

- The diagnosis of megaureter is based on clinical presentation and ultrasound before and after birth.
- The antenatal diagnosis of megaureter is based on ultrasound showing hydronephrosis.
- The diagnosis is confirmed by postnatal ultrasound.
- Grey-scale ultrasound:
  - Grey-scale ultrasound is the initial study obtained in any child in whom a urinary abnormality is suspected.
  - It provides useful anatomical detail of the renal parenchyma, collecting system, ureter and bladder.
  - Ultrasound offers a baseline of the degree of hydroureteronephrosis that can be used in serial follow-up.
- The finding of a ureter more than 7 mm in diameter confirm the diagnosis of a megaureter.



Figs. 7.15, 7.16, and 7.17 Abdominal and pelvic ultrasound showing primary megaureter. Note the markedly dilated ureter

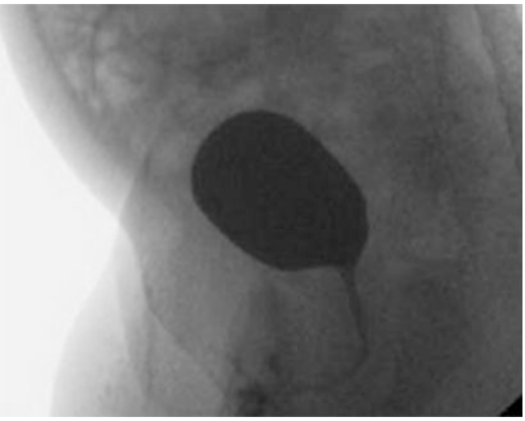
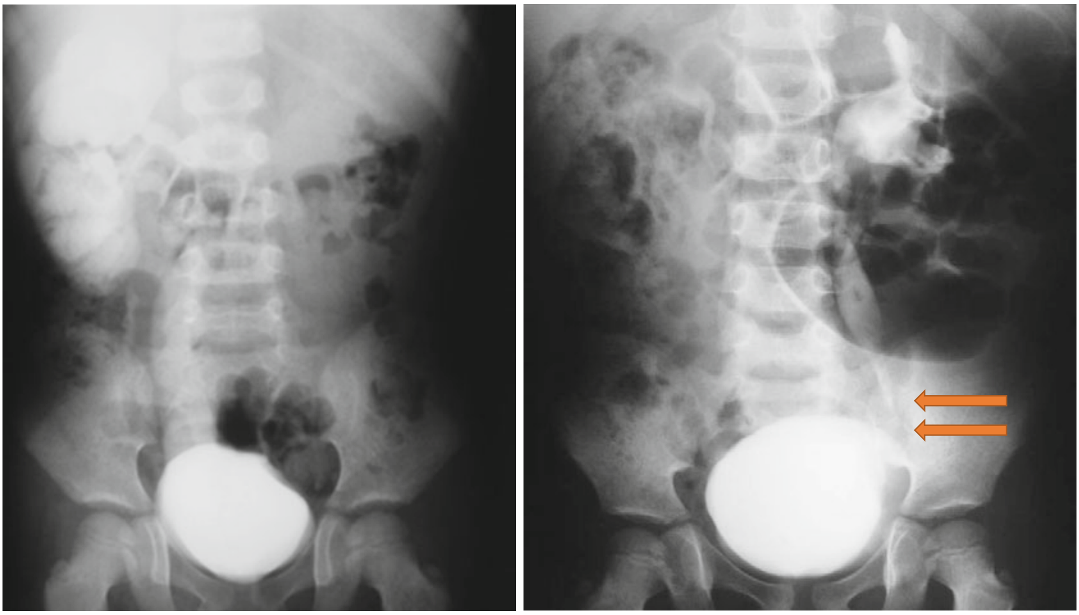


Fig. 7.18 A micturating cystourethrogram of the same patient showing no vesicoureteral reflux

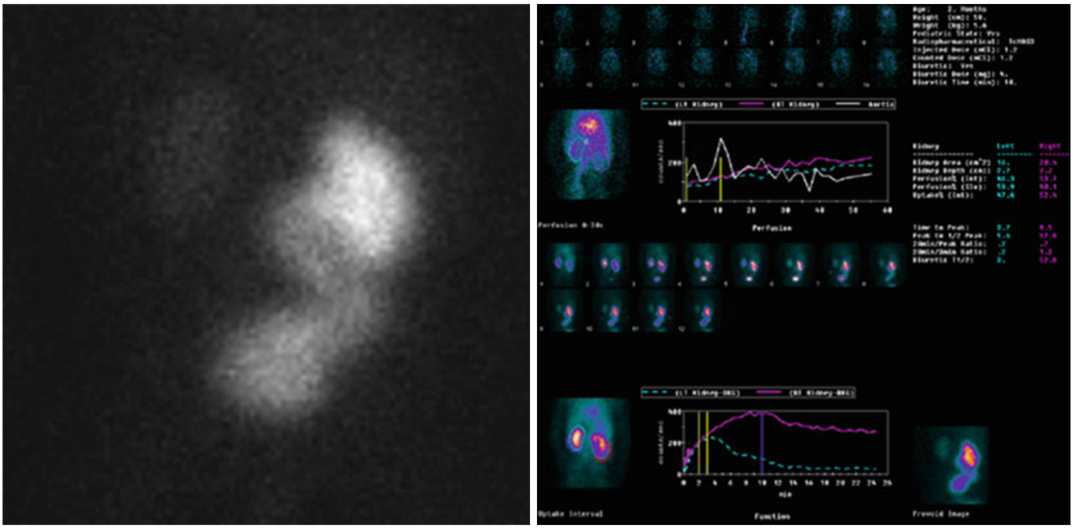
- In obstructive primary megaureter (Figs. 7.15, 7.16, 7.17, and 7.18):
  - The ureter tapers to a short segment of normal caliber or narrowed distal ureter, usually just above the vesicoureteric junction (VUJ).
  - The distal ureter above this narrowed segment is most dilated.
  - There is associated hydronephrosis.
  - Active peristaltic waves can be seen on ultrasound.
- The primary nature of megaureter must be confirmed and the secondary causes of megaureter must be excluded.
- Causes of secondary megaureter include:
  - Polyuria (diabetes insipidus)
  - Infection
  - Bladder outlet obstruction
  - Neuropathic bladder
  - Non-neurogenic voiding dysfunction
  - Infravesical obstruction or extrinsic lesions such as posterior urethral valve and severe urethral stricture.
- Doppler ultrasonography:
  - Doppler ultrasonography with a measurement of renal resistive index (RI) was recently introduced as a noninvasive method of diagnosing obstructive uropathy.



Figs. 7.19 and 7.20 Intravenous urography showing megaureter. Note the dilated ureter and back pressure on the kidney. Note also the tapered lower ureter in the second picture

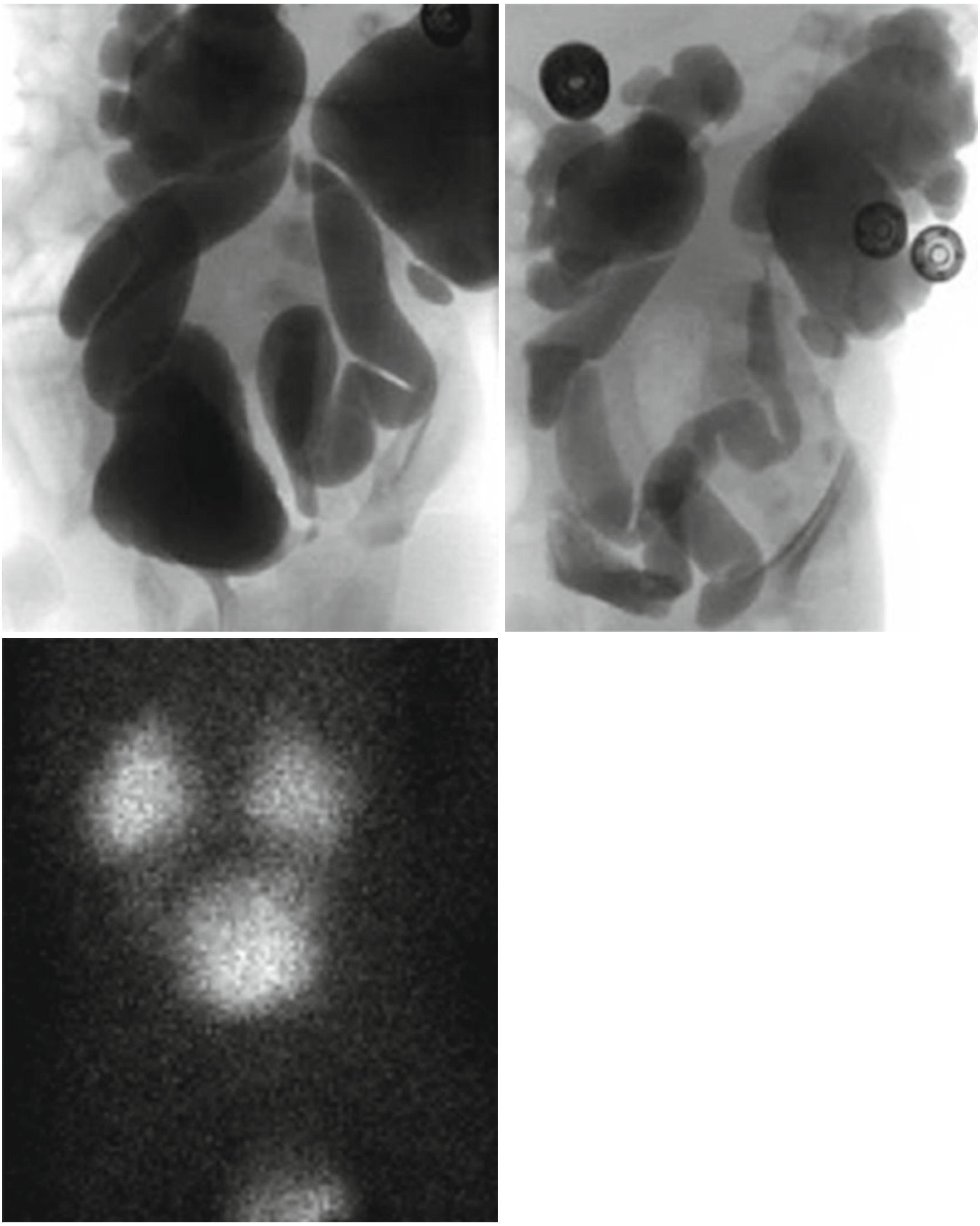
  - It has been shown that the RI is age-dependent and is commonly >0.70 in healthy children in the first year of life.
  - A normal RI exclude obstruction in the presence of a dilated collecting system.
  - An RI threshold of 0.70 gave a sensitivity of 82 %, a specificity of 63 % and an overall accuracy of 76 % in children with obstructive uropathy.
  - Several methods have been used to increase the diagnostic accuracy of RI.
  - The infusion of normal saline and administration of frusemide significantly decreased the RI of unobstructed kidneys and increased the RI of obstructed units.
  - The calculation of the difference between the RI of obstructed and unobstructed kidneys (ΔRI) strengthens the diagnosis.
  - Values of ΔRI of >0.06–0.10 are diagnostic of obstruction.
  - Recent reports showed a good correlation between the RI and DR. Therefore, the RI could be used for monitoring the dilated collecting systems under observation, obviating the need for frequent radioisotope scanning.

- The diagnosis is confirmed by intravenous urography (IVU) and radioisotope renography.
- Intravenous urography (IVU) (Figs. 7.19 and 7.20):
  - The anatomical detail provided by IVU is useful when the level of obstruction cannot be defined.
  - IVU usually shows the pathognomonic configuration of a dilated distal ureteric spindle, a less dilated proximal ureter and a dilated or relatively normal-appearing renal pelvis.
  - Caliectasis is either absent or mild.
  - IVU is currently rarely used as an initial step in the diagnosis of primary megaureter.
  - This is especially in neonates because of renal immaturity and bowel gas.
  - IVU should not be used before the age of 3–4 weeks and images taken 1 and 2 h after injection with contrast medium should be obtained.
- Radioisotope renography (Figs. 7.21 and 7.22):
  - A renogram provides anatomical information together with objective reproducible variables of both function and obstruction.

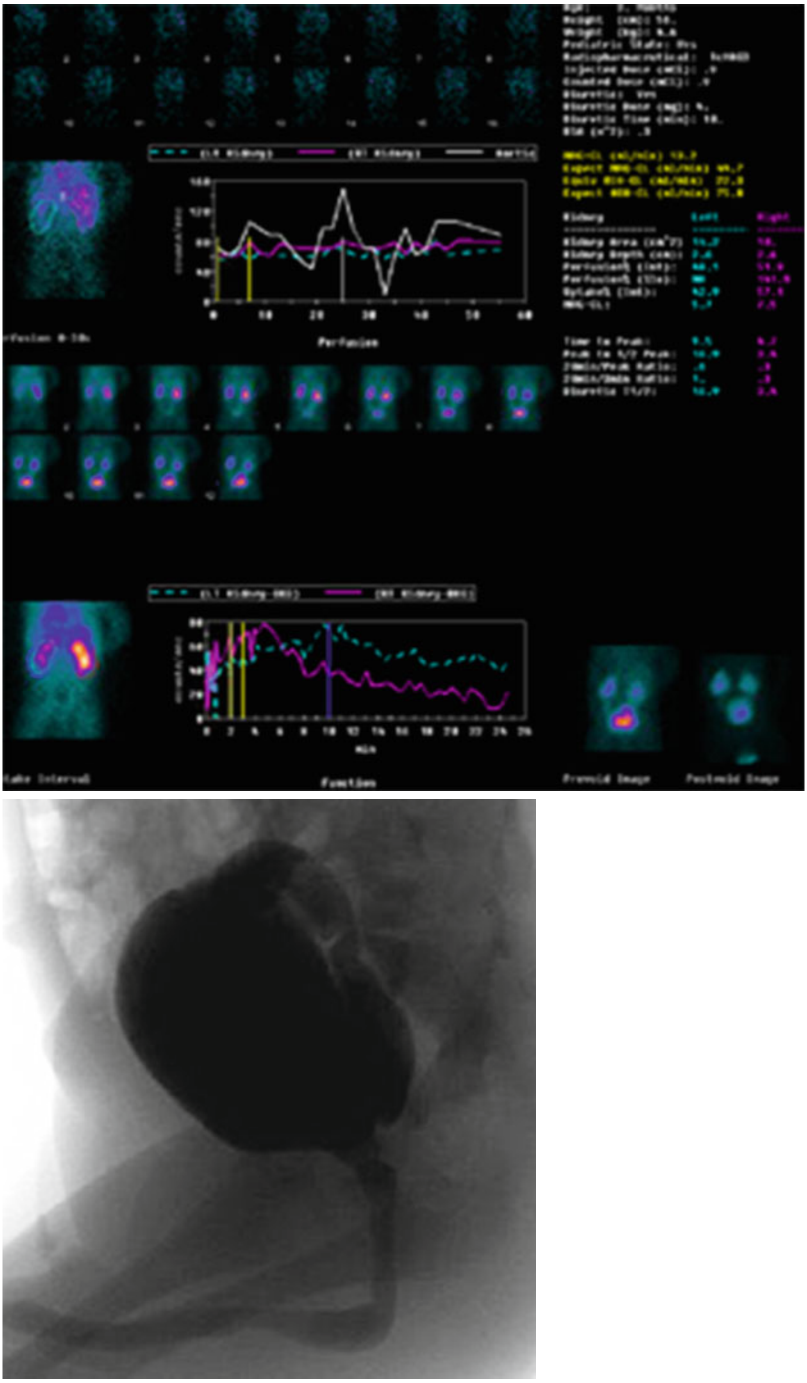


Figs. 7.21 and 7.22 Isotope renogram showing a dilated left ureter (megaureter) with evidence of obstruction

  - The most commonly used radionuclides are ^{99m}Tc-DTPA and -MAG3.
  - To assess obstruction, the diuretic renogram is used to detect the pattern of the frusemide washout curve and the half-time drainage ($T_{1/2}$).
  - In the standard diuretic renogram, frusemide is given 20 min after the injection of tracer. To decrease the false-positive results this technique was modified and frusemide is given 15 min before the injection of tracer. This is called F-15 instead of the usual F+20 technique.
  - Heyman and Duckett described the extraction factor (EF) as an estimate of single-kidney function in children during routine radionuclide renography with ^{99m}Tc-DTPA.
  - The EF is defined as the percentage uptake of radionuclide by the kidneys 2–3 min after injection with isotope.
  - The normal mean EF in the new-born is 1.5 % by each kidney, with an increase to 2.5 % occurring by the end of the first year of life.
  - The correlation coefficient of the EF with GFR is 0.92.
  - If renal function is normal by EF and/or equal to the contralateral undilated renal unit, the dilatation seen does not represent a functionally significant obstructive uropathy.
  - Measuring individual renal function to detect a decrease in function has been used by some to show the presence of obstruction.
  - The critical value of individual renal function below which obstruction is considered has varied among different studies.
  - Values of <30 %, <35 %, or <40 % have been suggested (normal 50 ± 5 %).
  - The failure of an expected improvement in renal function on further sequential radionuclide studies could be an indicator of the presence of obstruction.
- VUR is diagnosed using voiding cystourethrography (VCUG) (Figs. 7.23, 7.24, 7.25, 7.26, and 7.27).
  - Once ureteric dilatation is detected by US, VCUG is used to exclude reflux, and assess the quality of the bladder and urethra.
  - In refluxing primary megaureter, vesicoureteric reflux is demonstrated.
  - In non-refluxing unobstructed primary megaureter:
    - There is absent or only a minor degree of hydronephrosis.
    - Although rare, congenital megaureter may co-exist with congenital megacalyces, making assessment of hydronephrosis more difficult.



Figs. 7.23, 7.24, 7.25, 7.26, and 7.27 Micturating cystourethrograms, isotope renography and micturating cystourethrogram of a patient with severe bilateral vesicoureteric reflux but no posterior urethral valve


Perfusion
Function
Prevoid Image
Postvoid Image

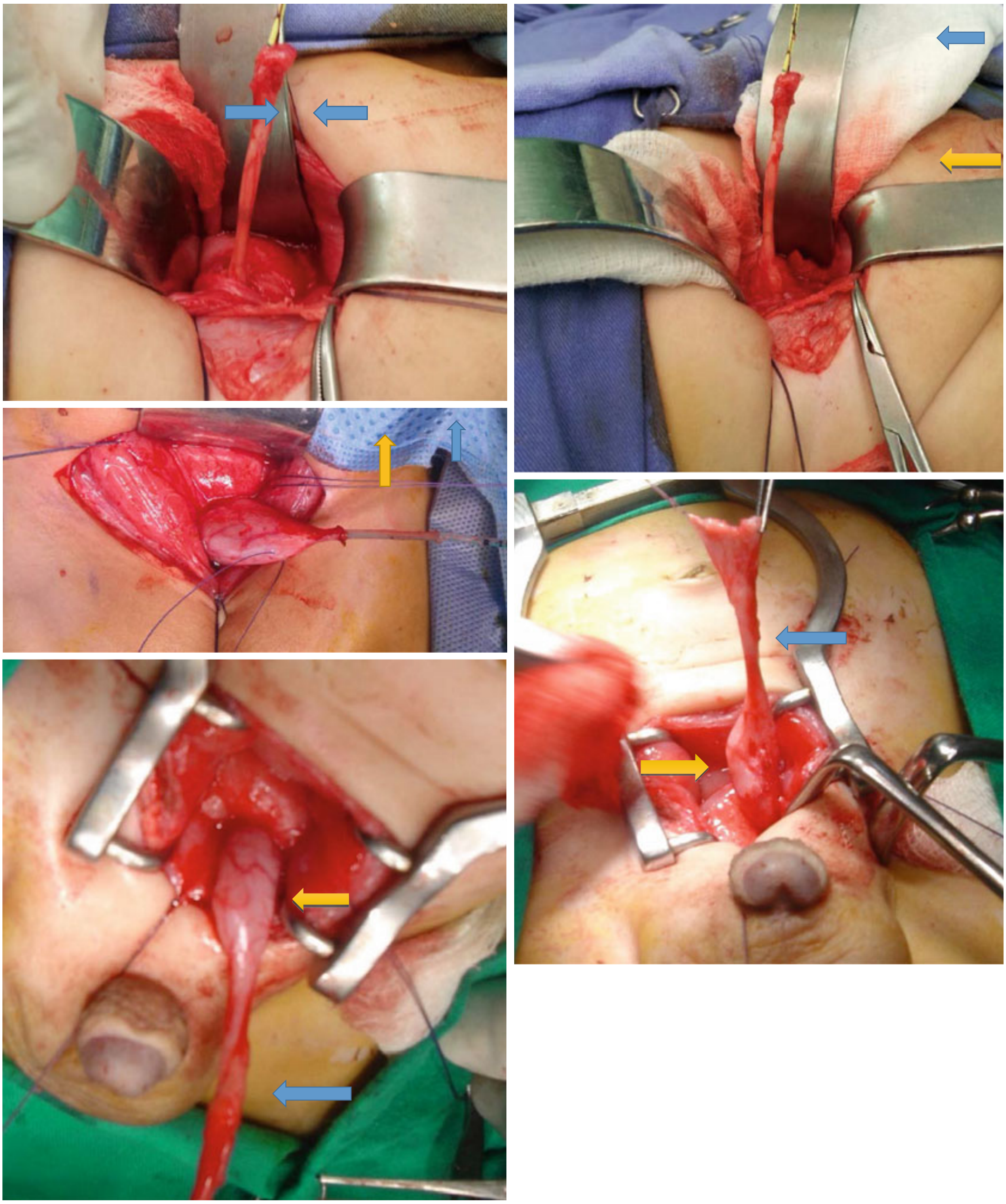
Figs. 7.23, 7.24, 7.25, 7.26, and 7.27 (continued)

  - Reflux and obstruction may coexist in a small proportion of patients; in such instances, the reflux is often the most obvious finding and concomitant obstruction may not be considered unless the possibility of a dual lesion is considered.
  - If a delayed film is obtained after the VCUG, poor drainage of one or both upper tracts may suggest associated VUJ obstruction.
  - This can be confirmed or excluded by further evaluation.
  - The final and most difficult step in the diagnosis is to differentiate between an obstructed and unobstructed megaureter.
  - Tests such as renal scintigraphy, Doppler ultrasonography (DUS) and pressure-flow studies (the Whitaker test) are useful investigations.
- The diagnosis in most cases is only possible by repeated investigations and comparivng changes of the variables during a longer follow-up.
- The Whitaker test:
  - The Whitaker test is currently rarely used in the diagnosis of children with megaureter.
  - It is invasive, does not measure function, submits the collecting system to unphysiological rates of flow and has a variable correlation with functional studies such as the diuretic renogram.

7.6 Treatment and Prognosis

- Increasing reports show that a considerable number of children with VUR or megaureters without reflux or obstruction may demonstrate improved renal function on radiography follow-ups, without surgical intervention.
- Nonoperative treatment however, requires close follow-up of patients with VUR or non-obstructed/non-refluxing megaureters.
- Nonoperative management of VUR and non-obstructed primary megaureter includes:
  - Antimicrobial prophylaxis
  - Treatment of voiding dysfunction
  - Follow-up regular imaging studies to assess renal growth, renal scarring, and possible resolution of pathology.
- Current recommendations for antibiotic prophylaxis in all patients with VUR include:
  - Antibiotic prophylaxis for children younger than 1 year with VUR and a history of febrile UTI, based on greater morbidity from recurrent UTI in this population.
  - The use of antibiotic prophylaxis in older children with VUR should be made on an individualized basis.
  - The use of antibiotic prophylaxis is most beneficial in:
    - Those with grade 3 or greater VUR
    - Girls
    - Those with a significant history of recurrent febrile UTIs
    - Those with bowel or bladder dysfunction
- Usually primary megaureter is asymptomatic and requiring no treatment.
- If complications occur or the degree of obstruction is marked then re-implantation following resection of the aganglionic segment may be performed.
- Megaureter secondary to severe VUR or obstruction is usually managed with ureteral reimplantation.
- Reimplantation techniques are similar to those used for correcting primary VUR.
- The megaureter can be mobilized via an intravesical, extravesical, or combined approach.
- Most megaureters will require tapering.
- The ureteral caliber can be reduced by:
  - Excising the distal redundant ureter (Hendren technique)
  - Plication (Kalicinski technique, Starr technique)
- Occasionally, the function of the kidney drained by a megaureter is severely impaired, and nephroureterectomy may be necessary.
- There have been reports of obstructive megaureters treated successfully by endoscopic dilation.
- The treatment of primary megureter depends on the type:

- Refluxing primary megaureter:
  - With the advent of antenatal ultrasound the management of refluxing primary megaureters changed in the past few years.
  - The previous recommendation for surgery in newborns and infants with grades 4 and 5 reflux is obsolete.
  - Medical management is appropriate during infancy and is continued if there is a trend to resolution.
  - Surgery is recommended for persistent high-grade reflux in older children.
- Nonrefluxing unobstructed primary megaureter:
  - Most patients who present with primary megaureter, particularly older children, clearly have the unobstructed variety.
  - Most of these patients remain asymptomatic without surgery, and expectant management results in an improvement in the degree of urinary tract dilatation and no deterioration of renal function.
  - This requires regular follow-up with antibiotic prophylaxis for urinary tract infections.
- Obstructed primary megaureter:
  - Many cases of primary megaureter diagnosed antenatally resolve spontaneously within the first 2 years of life, with the maturation of the urinary tract.
  - These are called 'primary dilated megaureter' by some authors to differentiate them from the real obstructive ones.
  - The presence of significant obstruction is an indication for early surgical correction to preserve renal function.
  - The goals of early surgery are:
    - To minimize renal damage from obstruction
    - To maximize the growth potential of the affected kidney
    - To prevent complications of primary megaureter, especially infection and stone formation.
  - However, presently there is no ideal method for assessing urinary tract obstruction, particularly in neonates and infants.
  - Therefore, the therapeutic recommendations for neonates with obstructed primary megaureter remain controversial.
  - During the past 10 years there has been an increasing trend towards conservative management.
  - In this approach of conservative management:
    - The patients are closely monitored including their symptoms
    - Imaging follow-up
    - Antibiotic prophylaxis
  - The frequency of imaging decreases as the urinary tract dilatation stabilizes.
  - Renal function is best assessed by renal scintigraphy
  - Antibiotic prophylaxis must be begun routinely soon after delivery in infants with prenatally detected hydroureteronephrosis.
  - Prophylaxis is continued after confirming the diagnosis of an obstructed primary megaureter.
  - When surgical repair is undertaken prophylaxis is continued until the obstruction is relieved and no reflux is detected.
  - The commonly used antibiotics for prophylaxis are:
    - Amoxicillin (15 mg/kg) once a day for infants <2 months
    - Trimethoprim (2 mg/kg) once a day for infants and children
  - Surgery is indicated in cases of:
    - Significant impairment to urine flow
    - Persistent pain
    - Pyelonephritis
    - Calculi
    - A decrease in renal function
- Principles of surgical treatment (Figs. 7.28, 7.29, 7.30, 7.31, and 7.32):
  - The ureter is mobilized as for reimplantation for VUR.
  - Resection of the distal ureter only is rarely sufficient to permit reimplantation.
  - Reduction of the caliber of the distal ureter is necessary.
  - Two methods can be used to remodel megaureters.
    - Hendren technique: Excision of the distal severely dilated and redundant ureter or those that are markedly thickened.



Figs. 7.28, 7.29, 7.30, 7.31, and 7.32 Clinical intraoperative photographs showing reimplantation of primary megaureters. Note the distal stenosed aperistalitic segment (⬅) and the proximally dilated ureter (⬅)

- Plication (Kalicinski technique, Starr technique): Plication of the distal ureter is used when there is less dilatation, but may produce a bulky and stiff ureteric segment.
  - Nonetheless, the frequency of postoperative reflux is no different between these methods.
  - In the past, reduction of the caliber of the distal and mid ureter was done, but

  currently reduction is limited to a section of ureter necessary to achieve an adequate length of intravesical tunnel.
  - Remodelled megaureters have generally been reimplanted using:
    - The standard Cohen cross-trigonal reimplantation
    - The Leadbetter-type reimplantation
    - The extravesical submucosal tunnel repairs
    - The extravesical seromuscular tunnel repair

7.7 Complications

- Ureteral reimplantation for megaureter repair is a very safe, reproducible, and successful procedure.
- The success in reimplanting remodelled megaureters, regardless of technique, is not as high as with undilated ureters.
- Furthermore, in the neonatal period the complication rate is higher for reimplantation of a dilated ureter, especially into a small bladder.
- The reported rate of reoperation for reflux or obstruction is about 12 %.
- The major complications are:
  - The development of ureteral obstruction (2–5 %)
  - VUR (approximately 10 %)
  - Diverticular formation
  - Ureteral obstruction is most likely the result of ureteral ischemia and subsequent fibrosis of an excisionally tapered segment.
  - Initial management of this complication is percutaneous or endoscopic dilatation and stenting of the stricture, but many such instances ultimately require open surgical revision.
  - If postoperative VUR is encountered, a reasonable treatment option is observation and antibiotic prophylaxis because many reflux cases resolve spontaneously.
- VUR is more likely to recur following reimplantation in cases in which bladder pressures are elevated (e.g. patients with untreated neuropathic bladders or voiding dysfunction).
- Careful assessment of voiding symptoms and a low threshold for urodynamic studies are crucial in the evaluation of patients with recurrent VUR.
- A renal ultrasound should be obtained following surgical correction of VUR to assess for obstruction.
- Because of the very high success rate of open ureteral reimplantation, a postoperative VCUG is performed only in select cases.
- Concomitant ipsilateral PUJ obstruction can be seen in infants with obstructive primary megaureter.
  - The preoperative diagnosis of both pathological conditions may be difficult.
  - When PUJ obstruction is present, the ipsilateral ureter is seldom seen on IVU.
  - The diagnosis is not made until a retrograde ureterogram is taken when the child is under anaesthesia for a pyeloplasty or when the ureter is seen to be dilated at the time of the pyeloplasty.
  - A preoperative renal scan is more helpful in this regard, as the obstructed ureter usually fills and is visualized as the obstructed pelvis drains.

Further Reading

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Vesicoureteral Reflux (VUR) in Children

8

8.1 Introduction

- Normally urine travels antegrade in one direction from the kidneys to the bladder via the ureters to the urinary bladder.
- Backward or retrograde flow of urine from the urinary bladder to the ureters or kidneys is prevented by a one way valve at the ureterovesical junction.
- The valve is formed by the oblique entrance of the distal ureter through the wall of the bladder. This creates a tunnel of about 1–2 cm into the wall of the urinary bladder.
- This tunnel is compressed as the bladder fills preventing backflow of urine.
- Vesicoureteral reflux (VUR) is a retrograde flow of urine from the bladder into the ureters/kidneys (Fig. 8.1).
- VUR occurs if the submucosal ureteric tunnel is short making the valve defective.
- VUR is one of the common conditions in infants and children.
- It has been estimated that 10 % of the population have some degree of VUR.
- VUR is more common among younger children because of the relative shortness of the submucosal ureteric tunnel.
- This susceptibility decreases as the child grows. This is as a result of growth and increase in the length of the ureteric tunnel.
- It has been estimated that in children under the age of 1 year with a urinary tract infection, 70 % of them will have VUR.
- This frequency decreases to 15 % by the age of 12 years.
- VUR is more commonly diagnosed in males antenatally, but in later life there is a definite female preponderance with 85 % of VUR cases being diagnosed in females.
- Overall prevalence of vesicoureteral reflux is unknown because many children are asymptomatic.
- A frequency of 1–2 % of VUR was reported among healthy children.

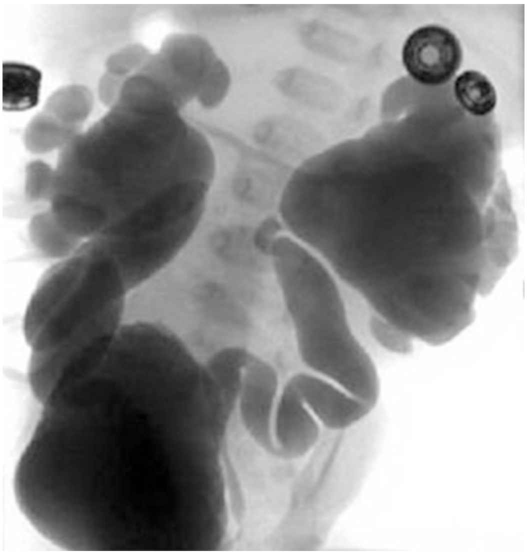

Fig. 8.1 A micturating cystourethrogram showing sever bilateral vesicoureteral reflux

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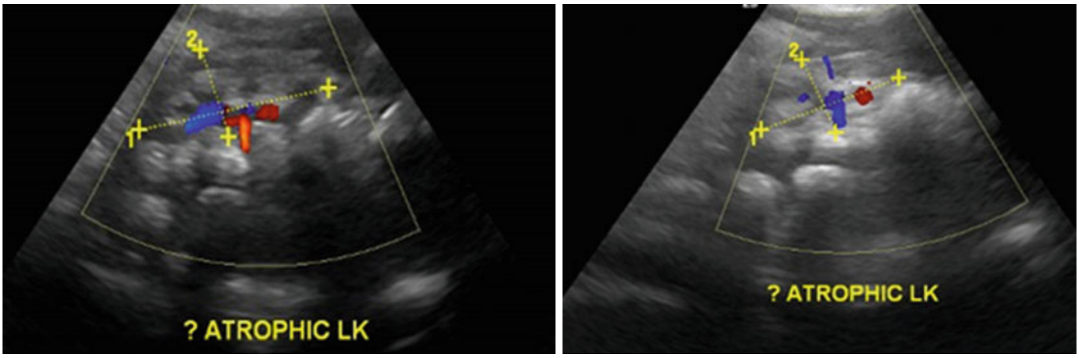
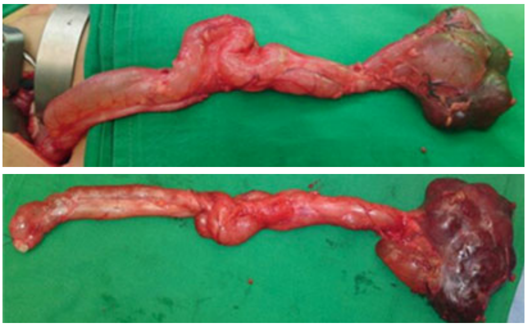
A.H. Al-Salem, *An Illustrated Guide to Pediatric Urology*, DOI 10.1007/978-3-319-44182-5_8

- The prevalence of VUR is higher among children with UTIs ranging from 15 to 70 %, depending on age.
- Approximately one third of patients diagnosed prenatally with hydronephrosis on ultrasonography, were found postnatally to have VUR.
- The incidence of reflux clearly is influenced by genetic factors, although the specific modes of inheritance is not defined.
  - Siblings of children with vesicoureteral reflux have a 25–33 % risk of also having VUR.
  - Offspring of parents with VUR have a 66 % risk of also having VUR.
  - This is higher in female offspring than male offspring.
- There are two distinct presentations of VUR:
  - Hydronephrosis, often prenatally identified using ultrasonography.
  - Clinical urinary tract infection.
- VUR can occur at any age but the average age at diagnosis of VUR is 2–3 years.
- It was suggested that early diagnosis of children with VUR may prevent episodes of UTI and renal scarring.
- Others feel that screening asymptomatic children will result in overtreatment of clinically insignificant VUR.
- VUR is more common in white children than in those of other races.
- VUR is less common in black children.
- VUR is ten times as common in white children as in black children.
- UTIs are known to be more common in girls than boys.
- Among all children with UTIs, boys are more likely to have vesicoureteral reflux than girls (29 % of males vs 14 % of females).
- Boys also tend to have higher grades of vesicoureteral reflux diagnosed at younger ages.
- Vesicoureteral reflux is more likely to spontaneously resolve in boys when compared to girls.
- VUR is more common among infants and progressively resolves in a substantial proportion of children.
- The prevalence of VUR decreases as children age.
- It was estimated that among patients who presented with UTI:
  - The prevalence of VUR was 70 % in patients younger than 1 year
  - The prevalence of VUR was 25 % in patients aged 4 years
  - The prevalence of VUR was 15 % in those aged 12 years
  - The prevalence of VUR was 5.2 % in adult patients.
- VUR is more prevalent in male newborns, but VUR seems to be five to six times more common in females older than 1 year than in males.
- The incidence decreases as patient age increases.
- Approximately three-quarters of children being treated for reflux are girls.
- The diagnosis of VUR depends on clinical suspicion and radiological investigations. The indications for radiological evaluation after the first attack of urinary tract infection include:
  - All children younger than 5 years.
  - Children of any age with febrile urinary tract infection.
  - Boys of any age with urinary tract infection.
- In patients with VUR, there is a close correlation between the frequency of urinary tract infection and the severity of VUR nephropathy.
- VUR nephropathy is considered the most common cause of childhood hypertension which is caused by increased renin secretion as a result of renal scarring (Figs. 8.2, 8.3, 8.4, and 8.5).
- The most devastating complication of VUR nephropathy is renal failure.
- Vesicoureteral reflux can be primary or secondary.
  - Primary vesicoureteral reflux results from a defect in the “flap valve” effect that normally prevents urine from flowing backward from the bladder into the ureters.
  - Secondary vesicoureteral reflux results from defective micturation secondary to obstruction in the urethra such as posterior



Figs. 8.2 and 8.3 Abdominal ultrasound showing atrophic left kidney secondary to VUR



Figs. 8.4 and 8.5 Clinical photographs showing hydroureters and dysplastic atrophic kidneys secondary to VUR

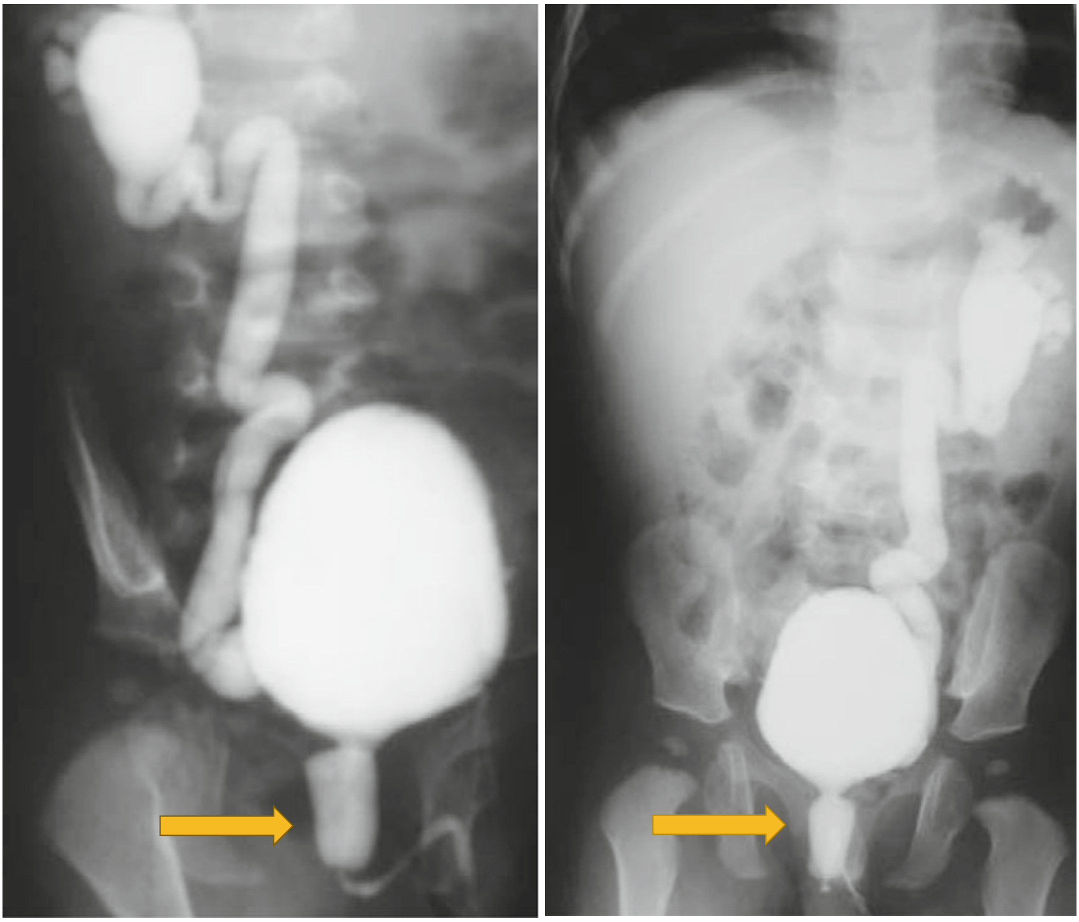
urethral valve or stricture or neurogenic bladder.

- More than 50 % of boys with posterior urethral valves have VUR. This can be unilateral or bilateral (Figs. 8.6 and 8.7).
- Dysfunctional voiding, with its inherent increase in intravesical pressure also results in VUR, even in otherwise healthy children.
- The incidence of VUR is much higher in children with febrile UTIs (i.e., 30–70 %).
- The incidence of prenatally diagnosed hydronephrosis caused by VUR ranges from 17 % to 37 % in the pediatric population.
- Approximately 20–30 % of children with VUR present with renal lesions (Fig. 8.8).
- The incidence of VUR in children and young adults with end-stage renal failure that necessitates dialysis or transplantation is about 6 %.
- VUR is the fifth-most-common cause of end-stage renal failure in children.

Hydronephrosis Diagnosed Prenatally

- 50 % are transient and resolve spontaneously.
- 15 % have hydronephrosis that persists but is not associated with urinary tract obstruction (non-refluxing, non-obstructive hydronephrosis).
- 35 % have a definite pathological cause for hydronephrosis. These include:
  - Pelvi-ureteric junction obstruction (11 %)
  - Vesicoureteral reflux (9 %)
  - Mega ureter (4 %)
  - Multicystic dysplastic kidney (2 %)
  - Ureterocele (2 %)
  - Posterior urethral valves (1 %)

- Vesicoureteral reflux (VUR) may be associated with:
  - Urinary tract infection (UTI)
  - Hydronephrosis
  - Abnormal kidney development (renal dysplasia)
  - Increased risk for pyelonephritis, hypertension, and progressive renal failure.
- VUR with concomitant UTI if not recognized and treated may lead to long-term effects on renal function and overall patient health.
- The severity of VUR greatly varies and thus may affect patients differently. Some individuals have a genetic predisposition to renal injury.
- Early diagnosis and vigilant monitoring of VUR are the cornerstones of management.



Figs. 8.6 and 8.7 Micturating cystourethrograms showing posterior urethral valve and VUR. Note the dilated posterior urethra

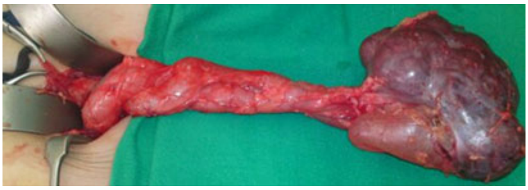
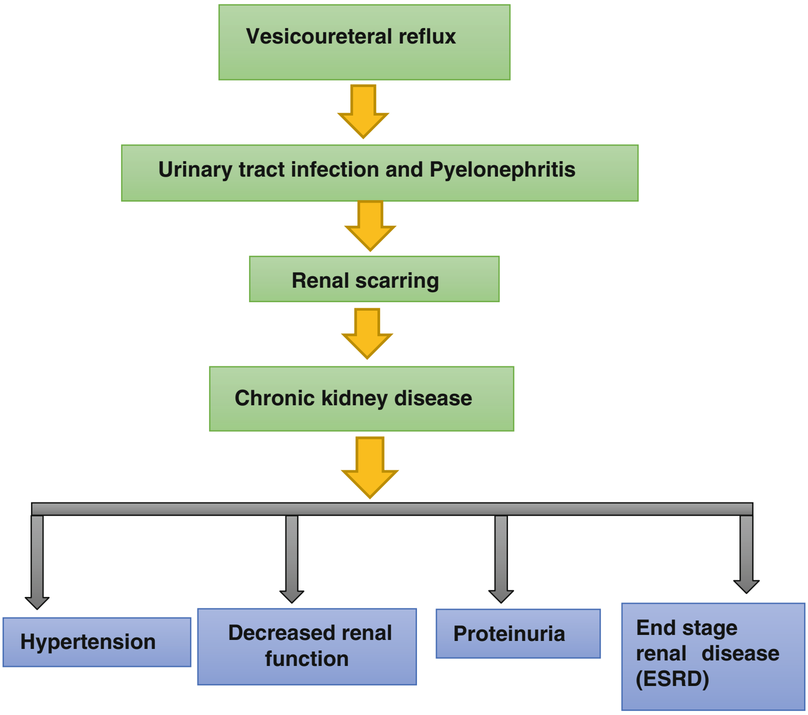


Fig. 8.8 A clinical intraoperative photograph showing a duplex system with hydroureter secondary to VUR and dysplastic kidney

8.2 Pathophysiology

- Anatomically, the ureter enters the urinary bladder through a hiatus in the detrusor muscle.
- The ureter is composed of three muscle layers: inner longitudinal, middle circular, and outer longitudinal.
- The outer longitudinal layer is enveloped by ureteral adventitia.
- The inner longitudinal layer of smooth muscle passes through the ureteral hiatus, continues distally beyond the ureteral orifice into the trigone, and intertwines with the smooth muscle fibers of the contralateral ureter, forming the Bell muscle of the trigone and posterior urethra.
- The middle circular muscle fibers, outer longitudinal muscle fibers, and periureteral adventitia merge with the bladder wall in the upper part of the ureteral hiatus to form the Waldeyer sheath.
- This sheath attaches the extravesical portion of the ureter to the ureteral hiatus.
- The normal valve mechanism of the ureterovesical junction includes:
  - Oblique insertion of the intramural ureter

  - Adequate length of the intramural portion of the ureter
  - Strong detrusor support.
- The distal ureter then passes obliquely through a submucosal tunnel before opening into the bladder lumen via the ureteral orifice.
- This creates a tunnel of about 1–2 cm long into the wall of the urinary bladder.
- This tunnel is compressed as the bladder fills and the intravesical pressure increases preventing backflow of urine from the urinary bladder to the upper urinary tract.
- The length of this submucosal tunnel and the muscular coat is important in creating a one-way valve preventing backflow of urine.
- If the length of the submucosal tunnel is short or if the muscular backing is inadequate, the one-way valve mechanism becomes incompetent, resulting in reflux.
- It was found that the ratio of tunnel length to ureteral diameter is important in the one-way mechanism.
- A ratio of at least 5:1 is important to ensure a competent one-way valve to prevent reflux.
- An abnormal short intramural tunnel results in a malfunctioning flap-valve mechanism and urine tends to reflux up the ureter and into the collecting system (VUR).
- It was estimated that refluxing ureters have an intramural tunnel length–to–ureteral diameter ratio of 1.4:1.
- When this protective mechanism fails, VUR occurs.
- VUR will lead to ascending infection and pyelonephritis which are the essential causes of reflux nephropathy.


Vesicoureteral reflux
Urinary tract infection and Pyelonephritis
Renal scarring
Chronic kidney disease
Hypertension
Decreased renal function
Proteinuria
End stage renal disease (ESRD)

- A close correlation was established between the frequency of UTI and severity of reflux nephropathy in patients with vesicoureteral reflux.
- Renal scarring may result from a single episode of pyelonephritis, especially in very young patients.
- Most renal scarring tends to occur at the renal poles, where the anatomy of the renal papillae permits backflow of urine into the collecting ducts.
- This phenomenon is referred to as intrarenal reflux and gives pathogenic bacteria access to the renal tubules.
- The human kidney contains two types of renal papillae:
  - Simple (convex) papilla
  - Compound (concave) papilla
- Compound papillae are commonly seen at the polar regions of the kidney, whereas simple papillae are located at nonpolar regions of the kidney.
- Approximately 66 % of human papillae are simple (convex) and 33 % are compound (concave).
- Intrarenal reflux or retrograde movement of urine from the renal pelvis into the renal parenchyma is a function of intrarenal papilla.
- Simple papillae possess oblique, slit like, ductal orifices that close upon increased intrarenal pressure and do not allow intrarenal reflux.
- Compound papillae possess gaping orifices that are perpendicular to the papillary surface that remain open upon increased intrarenal pressure allowing free intrarenal reflux.
- Renal scars are often present at initial diagnosis of VUR and usually develop during the first years of life.
- Persistent intrarenal reflux causes renal scarring and eventual reflux nephropathy.
- Reflux nephropathy leads to:
  - Impaired renal function
  - Hypertension
  - Proteinuria
  - End stage renal disease
- These effects depend on the type of urine.
- Two types of urine may reflux and enter the renal papillae: infected urine or sterile urine.
- Intrarenal reflux of infected urine is primarily responsible for the renal damage.
- The presence of bacterial endotoxins (lipopolysaccharides) activates the host's immune response and a release of oxygen free radicals. The release of oxygen free radicals and proteolytic enzymes results in fibrosis and scarring of the affected renal parenchyma during the healing phase.
- This initial scar formation at the infected polar region distorts the neighboring papillae and converts simple papillae into compound papillae.
- Compound papillae, in turn, perpetuate further intrarenal reflux which further increases renal scarring.
- Compound papillae are most commonly found at the renal poles, where renal scarring is most commonly observed.
- These focal areas of renal scars can be detected by Renal scan (DMSA).
- Diffuse lesions on renal scan are believed to be due to renal dysplasia, which results from abnormal kidney development.
- It is observed in patients who have higher grades of reflux (IV and V) and who have never had any evidence of UTI or pyelonephritis.
- Intrarenal reflux of sterile urine (under normal intrapelvic pressures) has not been shown to produce clinically significant renal scars.
- Treatment with long-term low-dose antibiotic prophylaxis to maintain sterile urine appears to inhibit renal scarring in children with uncomplicated VUR.
- Thus, renal scars appear to develop only in the presence of intrarenal reflux of infected urine.
- One exception to this is intrarenal reflux of sterile urine in the presence of abnormally high intravesical pressures.
- Abnormally high intravesical pressure is seen in:
  - Bladder outlet obstruction (functional or anatomical)
  - Nonneurogenic neurogenic bladder, or Hinman syndrome
  - Gastrointestinal dysfunction including chronic constipation
  - Children with overactive bladder (e.g. detrusor hyperreflexia, detrusor instability)
- Renal lesions are associated with higher grades of reflux.
- Renal units with low-grade reflux may grow normally, but high grades of reflux are associated with renal growth retardation.

- Pyelonephritic scarring may, over time, cause serious hypertension due to activation of the renin-angiotensin system.
- Scarring related to VUR is one of the most common causes of childhood hypertension.
- It was estimated that hypertension develops in 10 % of children with unilateral scars and in 18.5 % with bilateral scars.
- Approximately 4 % of children with VUR progress to end-stage renal failure.

8.3 Classification of VUR

- VUR is classified into two types:
  - Primary VUR:
    - This is the most common type of VUR (Figs. 8.9 and 8.10).
- It is caused by a defect in the development of the valve-like effect at the uretrovesical junction with insufficient submucosal ureteric length relative to its diameter.
    - This type is usually detected antenataly or shortly after birth.
    - Primary reflux is vesicoureteral reflux in an otherwise normally functioning lower urinary tract.
    - This is precipitated by a congenital defect.
    - Lack of longitudinal muscle of the intravesical ureter result in anomaly of the ureterovesicular junction (UVJ).
- This defect causes inadequacy of the valvular mechanism and failure of its function as a one-way valve leading to backflow of urine from the urinary bladder to the ureters and kidneys.
- This defect can be unilateral or bilateral (Fig. 8.11)

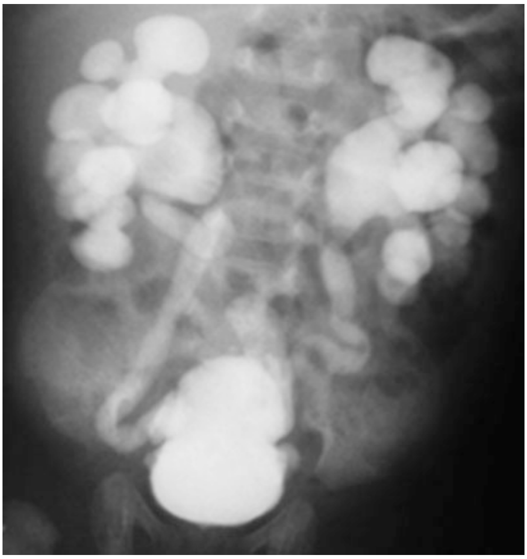
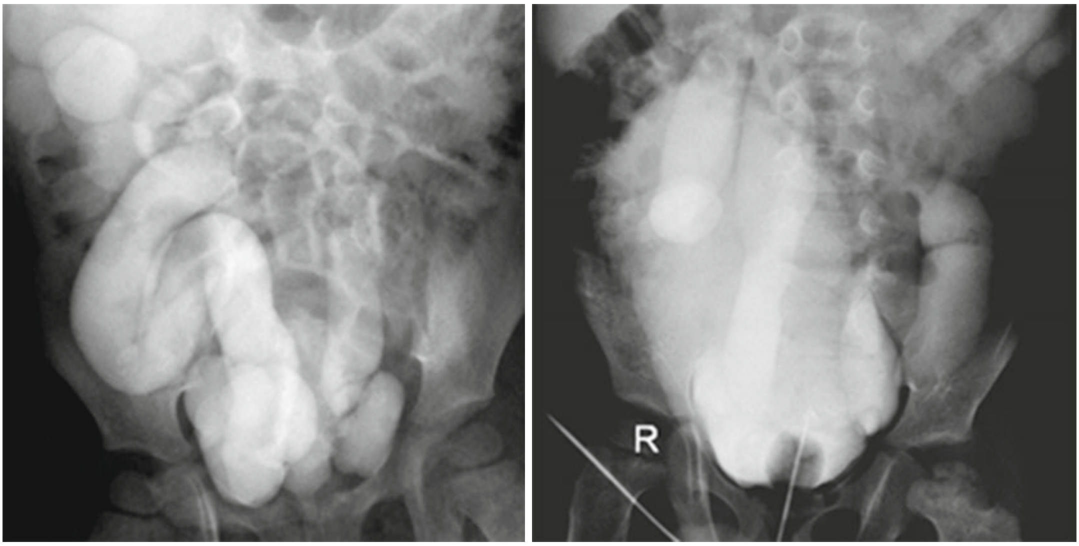
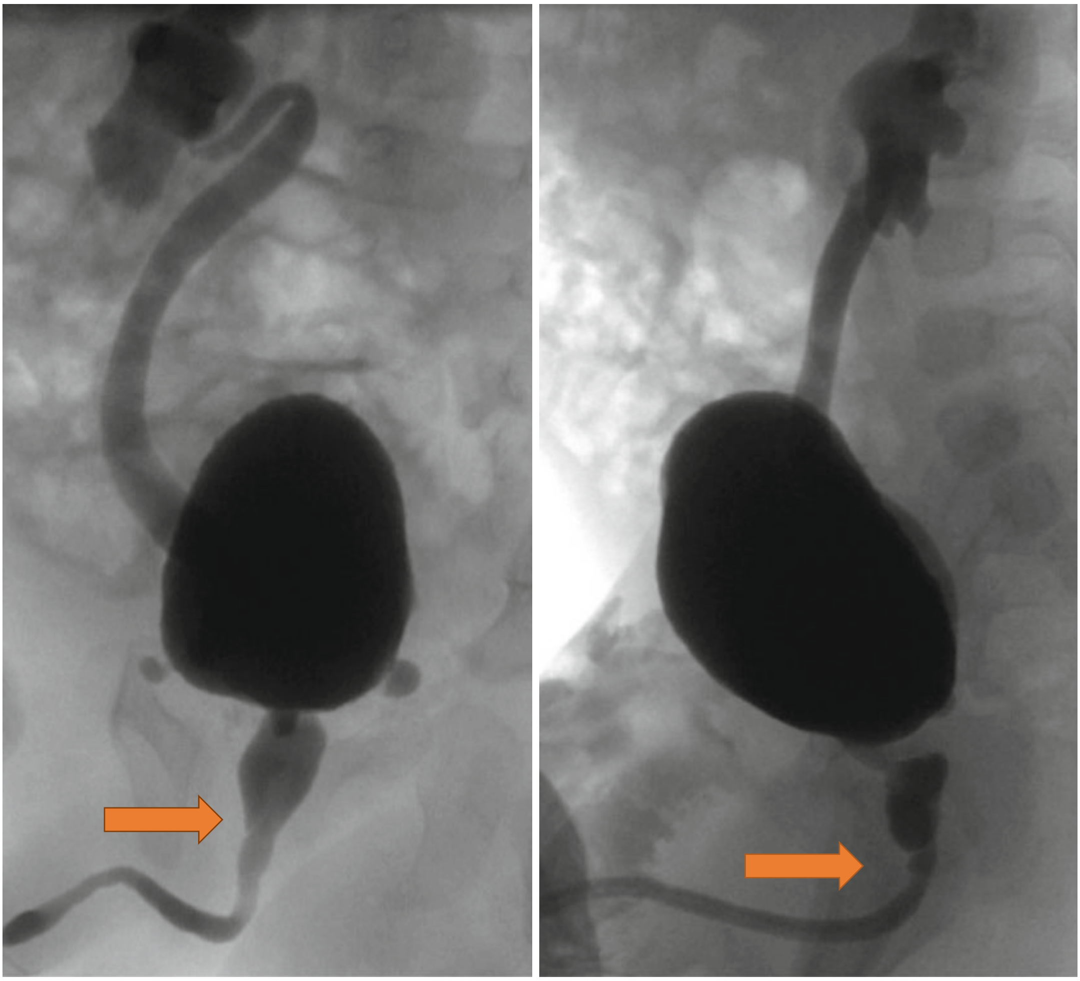


Fig. 8.11 A micturating cystourethrogram showing bilateral VUR

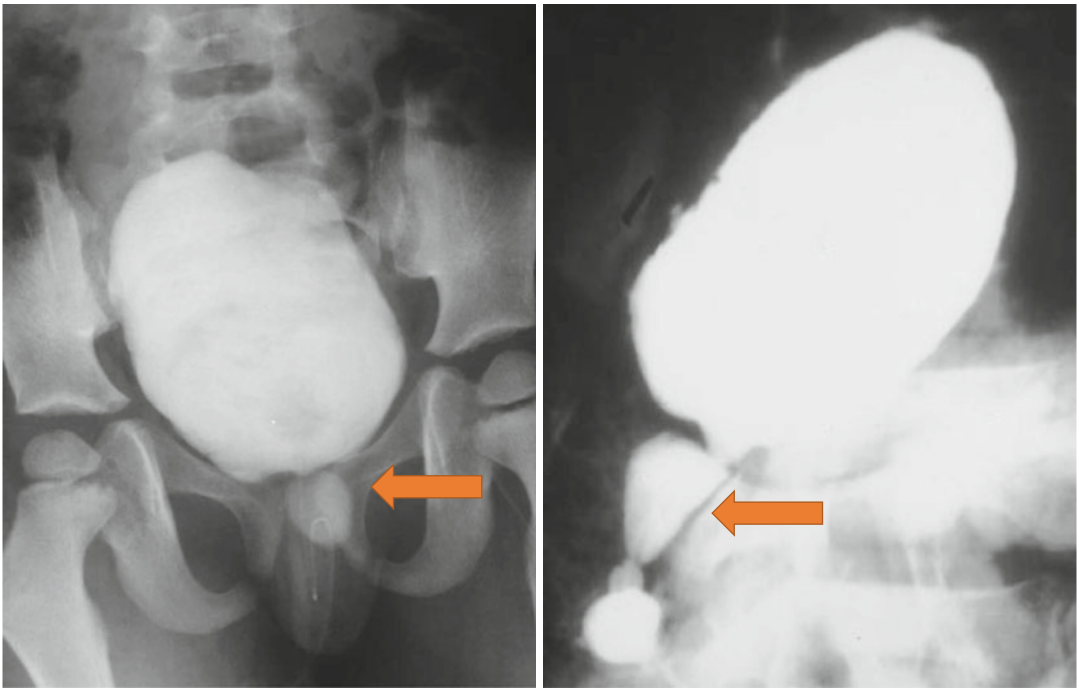


Figs. 8.9 and 8.10 Micturating cystourethrogram showing severe VUR. Note the dilated tortous ureters

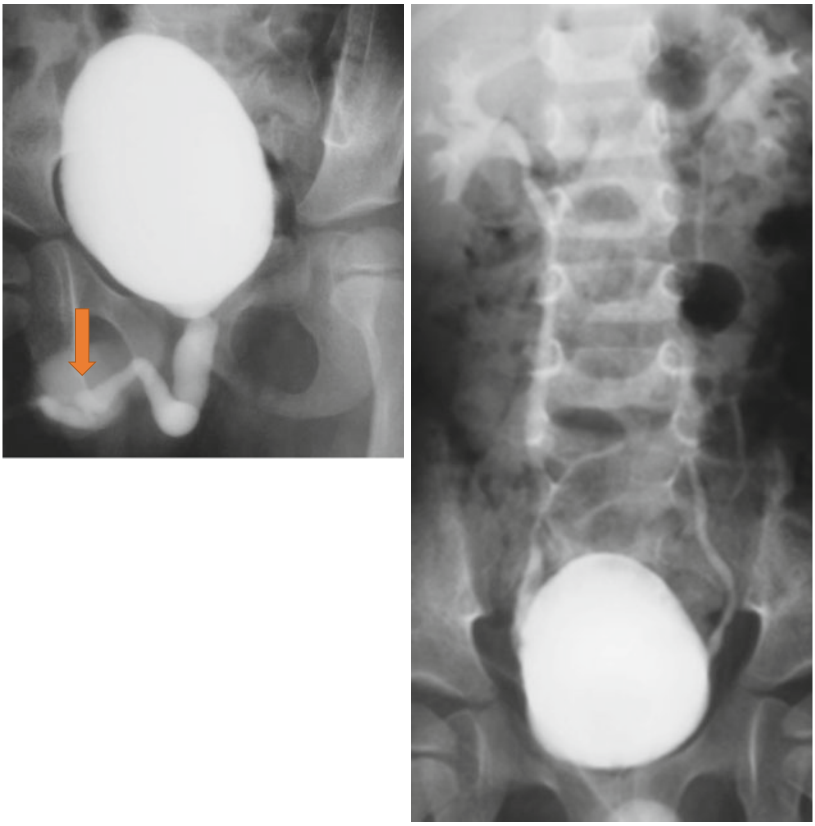


Figs. 8.12 and 8.13 Micturating cystourethrograms showing posterior urethral valve and associated secondary VUR. Note the dilated posterior urethra and the diverticulae from the urinary bladder

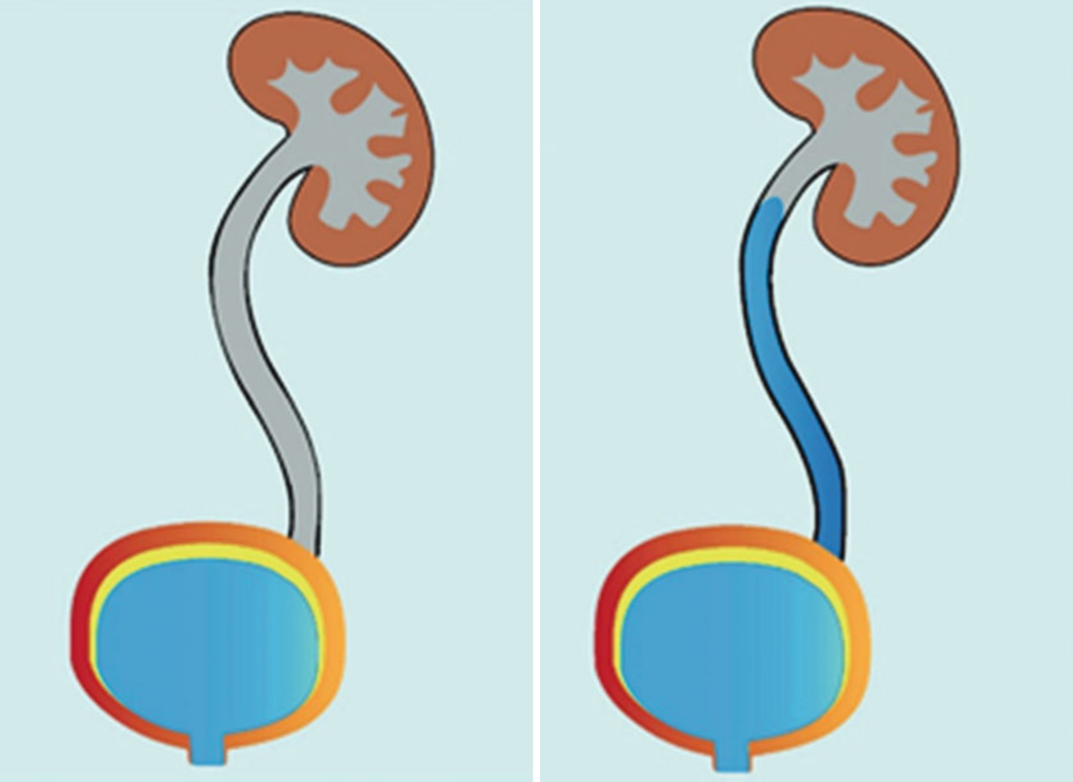
  - Secondary VUR:
    - Secondary reflux is vesicoureteral reflux that is associated with or caused by an obstructed or poorly functioning lower urinary tract.
    - In this category the valvular mechanism is intact and healthy to start with but becomes overwhelmed by raised intravesicular pressures associated with obstruction.
    - This leads to distortion of the uretero-vesical junction and failure of its function as a one-way valve.
    - Secondary VUR can be further divided into anatomical and functional groups.
    - This is seen in those with posterior urethral valves (anatomical) or a neurogenic bladder (functional).
    - The main causes of secondary VUR are:
      - Posterior urethral valves (Figs. 8.12, 8.13, 8.14, and 8.15)
      - Neurogenic bladder
      - Urethral stricture (Figs. 8.16 and 8.17)
      - Meatal stenosis
- VUR is also classified into five grades:
  - Voiding cystourethrography (VCUG) is the criterion standard in diagnosis of VUR, providing precise anatomic detail and allows grading of the reflux.



Figs. 8.14 and 8.15 Micturating cystourethrograms showing posterior urethral valve without VUR



Figs. 8.16 and 8.17 Micturating cystourethrogram showing urethral stricture secondary to hypospadias repair and secondary mild VUR



Figs. 8.18 and 8.19 Diagrammatic representation of grade I VUR. The *blue* color represents urine in the ureter

- The International Classification System for VUR is based on the radiographic appearance of the ureter, renal pelvis and calyces on a voiding cystogram.
- It is important to note that the presence of a severe reflux on one side may hide a milder degree of reflux on the other side in those with bilateral reflux.
- In these cases reflux on the milder side may appear postoperatively following treatment of the more severely affected side.
- This is one of the causes of appearance of reflux on the contralateral side following successful treatment of the severely affected side.
- The International Classification System for VUR is as follows:
  - Grade I – Reflux into nondilated ureter (Figs. 8.18, 8.19, and 8.20)
  - Grade II – Reflux into renal pelvis and calyces without dilation (Figs. 8.21 and 8.22)
  - Grade III – Reflux with mild to moderate dilation and minimal blunting of fornices (Figs. 8.23, 8.24, and 8.25)
  - Grade IV – Reflux with moderate ureteral tortuosity and dilation of pelvis and calyces (Figs. 8.26, 8.27, and 8.28)

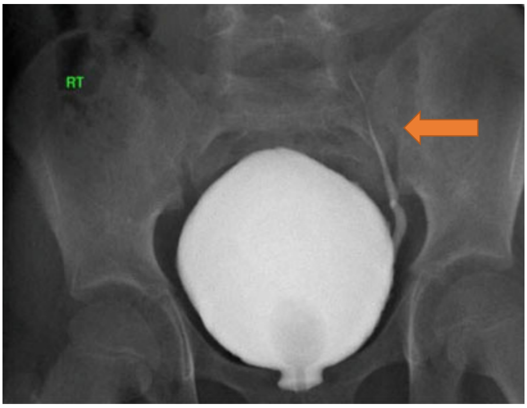
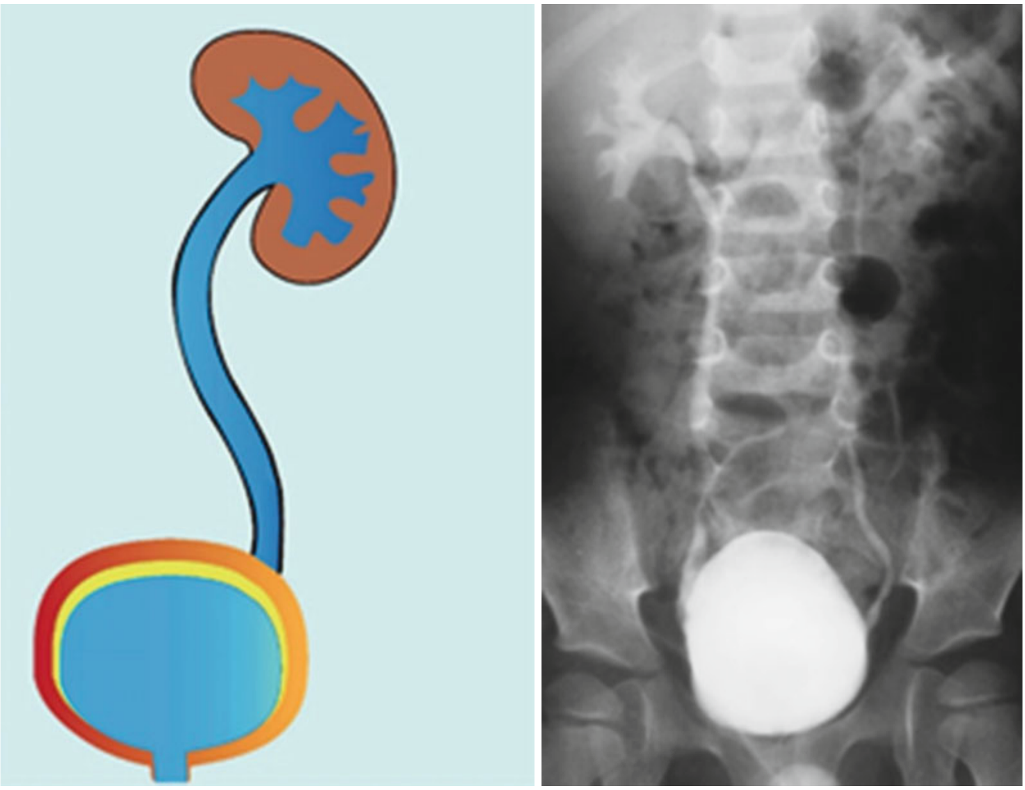


Fig. 8.20 A micturating cystourethrogram showing grade I VUR



Figs. 8.21 and 8.22 Diagrammatic representation of grade II VUR and a micturating cystourethrogram showing grade II VUR

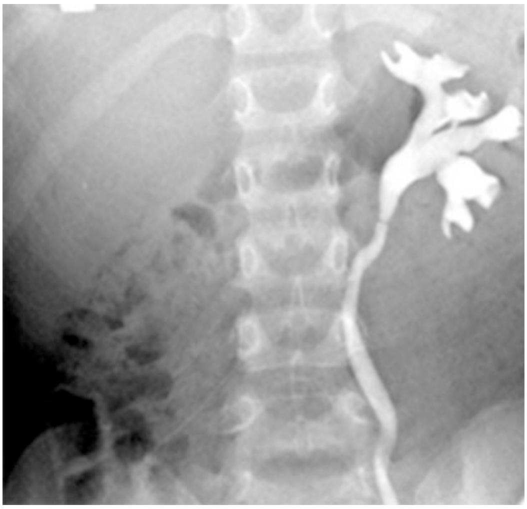
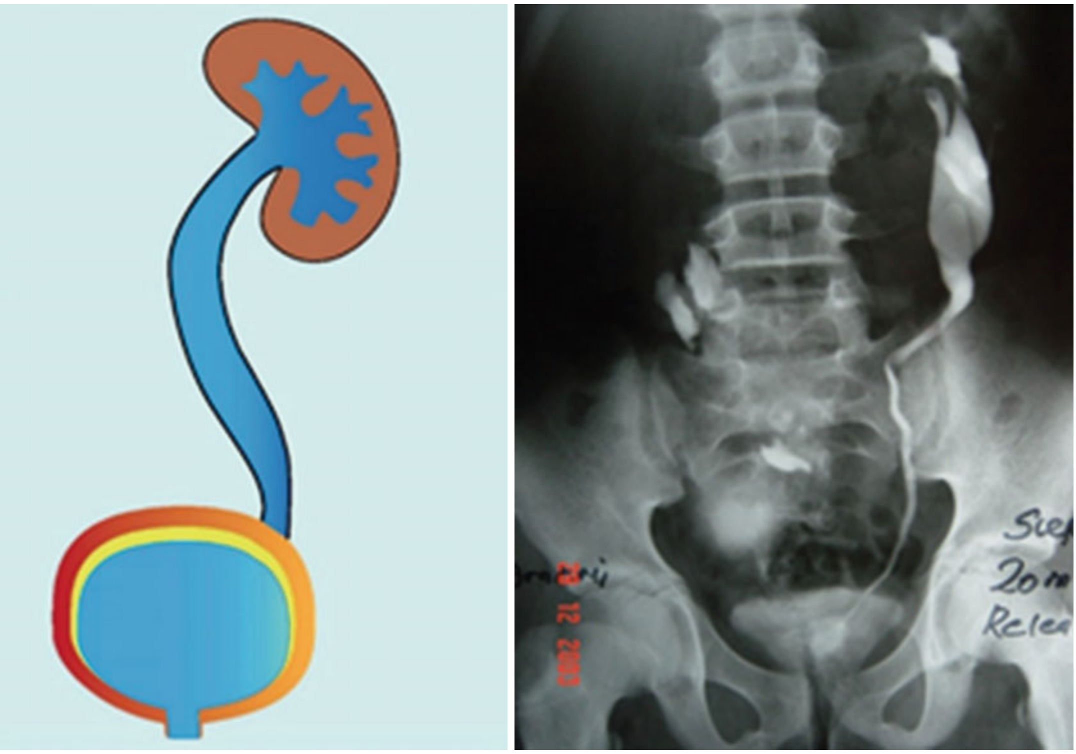


Fig. 8.23 A micturating cystourethrogram showing grade III VUR

- Grade V – Reflux with gross dilation of ureter, pelvis, and calyces, loss of papillary impressions, and ureteral tortuosity (Figs. 8.29, 8.30, and 8.31)

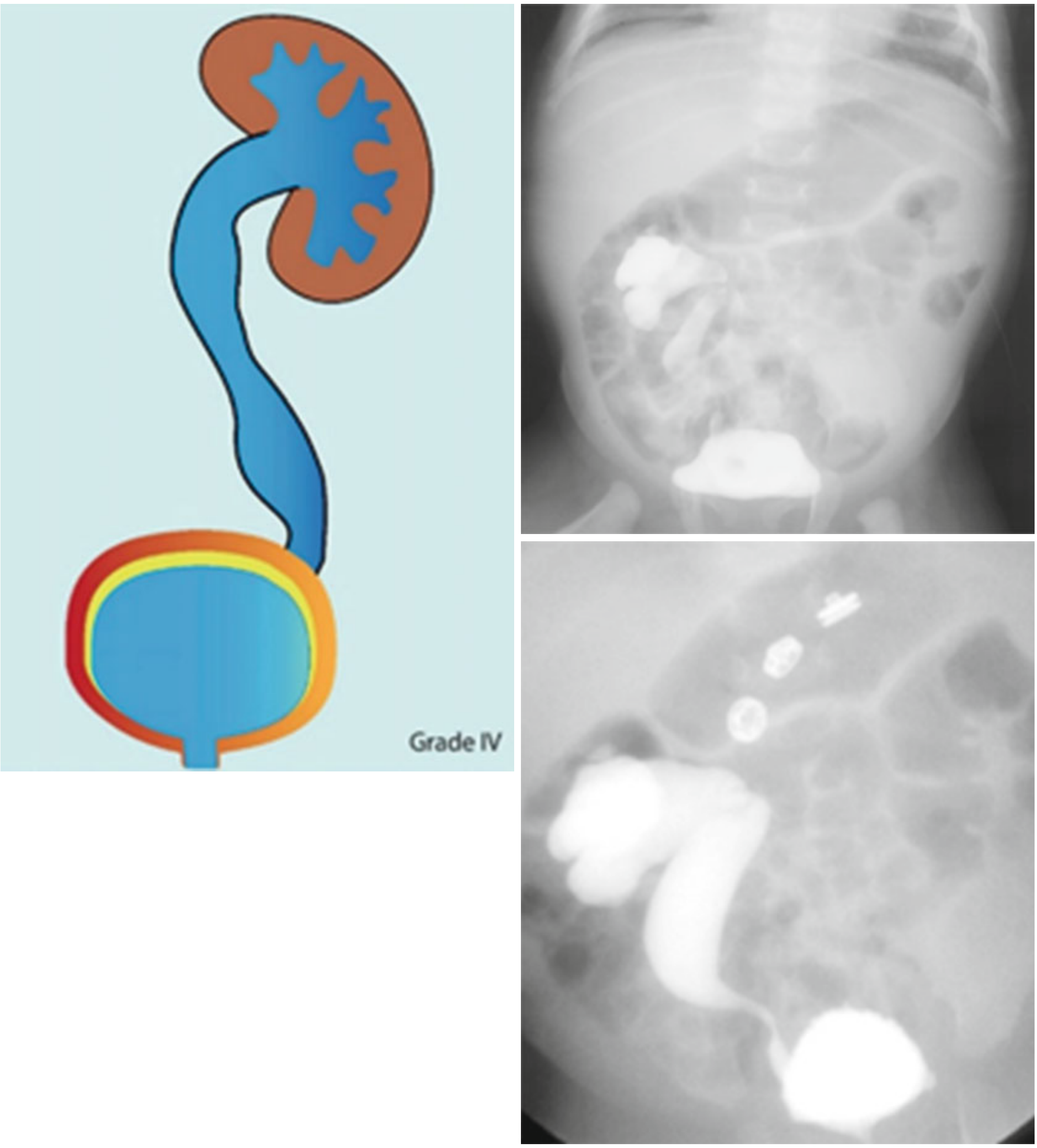
8.4 Etiology of VUR

- VUR is prevented by a one way valve like effect at the uretero-vesical junction.
- This is attributed to several factors including:
  - The oblique entrance of the ureter into the urinary bladder
  - The submucosal tunnel through which the ureter enter into the urinary bladder
  - The ureter's muscular attachments
- Failure of this mechanism will result in retrograde flow of urine.
- VUR is divided into two types based on etiology:
  - Primary VUR
  - Secondary VUR
- Primary VUR:
  - Primary VUR is the most common form of reflux
  - It is due to incompetent or inadequate ureterovesical junction (UVJ)



Figs. 8.24 and 8.25 Diagrammatic representation of grade III VUR and a micturating cystourethrogram showing grade III VUR. Note the hydronephrotic pelvic right kidney

  - The exact cause of the defect in primary VUR is unknown
  - This may be secondary to an abnormally short intravesical ureteric segment or abnormal surrounding muscles.
  - Other factors that contribute to the etiology of primary VUR include:
    - The existence of a strong genetic component is supported by the high rate of reflux in relatives of patients with reflux, but the mechanism of transmission is not clear.
    - The possibility of urinary tract infection as a cause of VUR is not clear and many think that UTI and VUR are independent variables. Urinary tract infections may cause reflux due to the elevated pressures associated with inflammation.
- Secondary VUR:
  - Secondary VUR is reflux that is associated with or caused by an obstructed or poorly functioning lower urinary tract.
  - This is seen in children with congenital bladder outlet obstruction and neurogenic bladder (Figs. 8.32 and 8.33).
  - More than 50 % of boys with posterior urethral valves have vesicoureteral reflux (Figs. 8.34 and 8.35).
  - In these patients, VUR can be unilateral or bilateral
  - Other causes include urethral or meatal stenosis
  - Bladder instability, neurogenic bladder and non-neurogenic bladder
  - Dysfunctional voiding, with its inherent increase in intravesical pressure, is a cause reflux, even in otherwise healthy children.
  - The combination of high-pressure voiding and vesicoureteral reflux increases the risk of pyelonephritis beyond that of the child with low-pressure reflux.
  - A unique group of children presents with dysfunctional elimination, which consists



Figs. 8.26, 8.27, and 8.28 Diagrammatic representation of grade IV VUR and Micturating cystourethrograms showing grade IV VUR

of a symptom complex heralded by infection, severe constipation, and daytime wetting (Figs. 8.36, 8.37, and 8.38).

– Some of these children have infrequent voiding and incomplete bladder emptying, which further increases the likelihood of UTI.

– Hardikar syndrome: This include:
  - Vesicoureteral reflux
  - Hydronephrosis
  - Cleft lip and palate
  - Intestinal obstruction and other symptoms

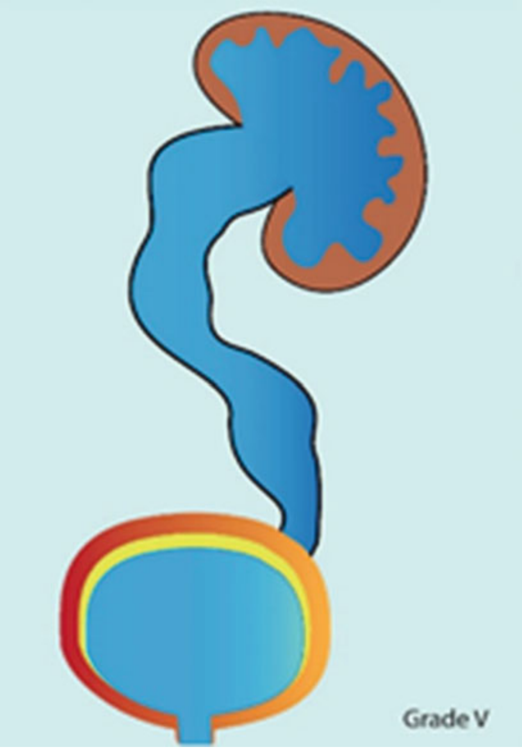
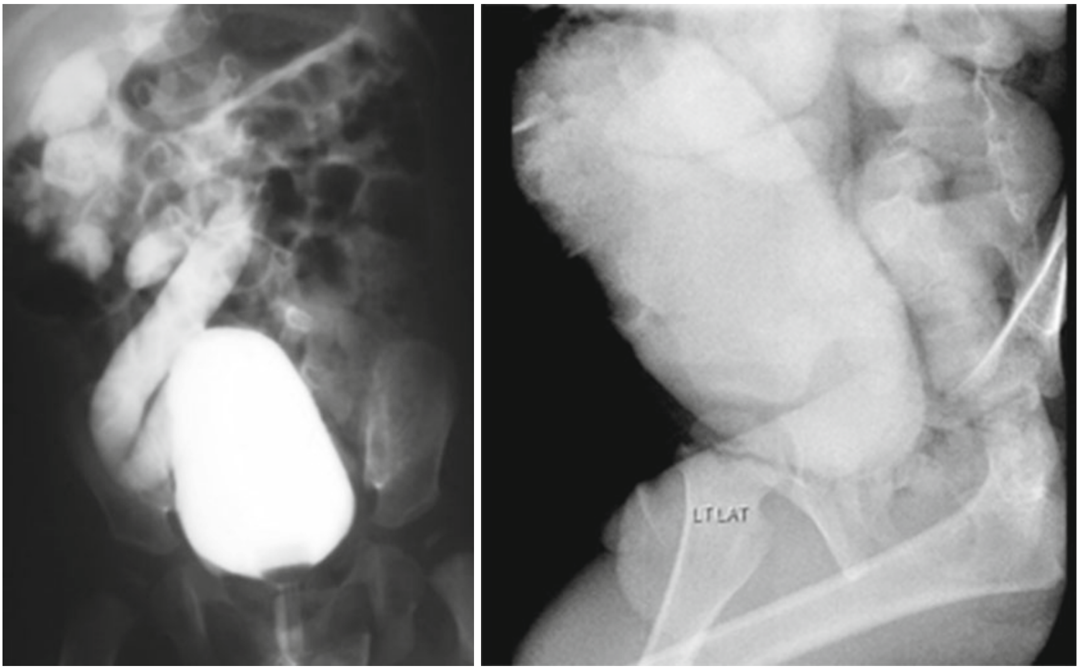


Fig. 8.29 Diagrammatic representation of grade V VUR

8.5 Clinical Features

- VUR cannot be diagnosed prenatally.
- VUR however may be suspected in the prenatal period, when transient dilatation of the upper urinary tract is noted in conjunction with bladder emptying.
- Approximately 10 % of neonates diagnosed prenatally with dilatation of the upper urinary tract will be found to have VUR postnatally.
- In general, VUR is almost always asymptomatic.
- VUR does not cause any specific signs or symptoms unless complicated by UTI (febrile UTI).
- Most infants and children with vesicoureteral reflux (VUR) present in one of two distinct groups:
  - The first group presents with hydronephrosis, often prenatally identified using ultrasonography.
  - The second group presents with urinary tract infection (UTI).

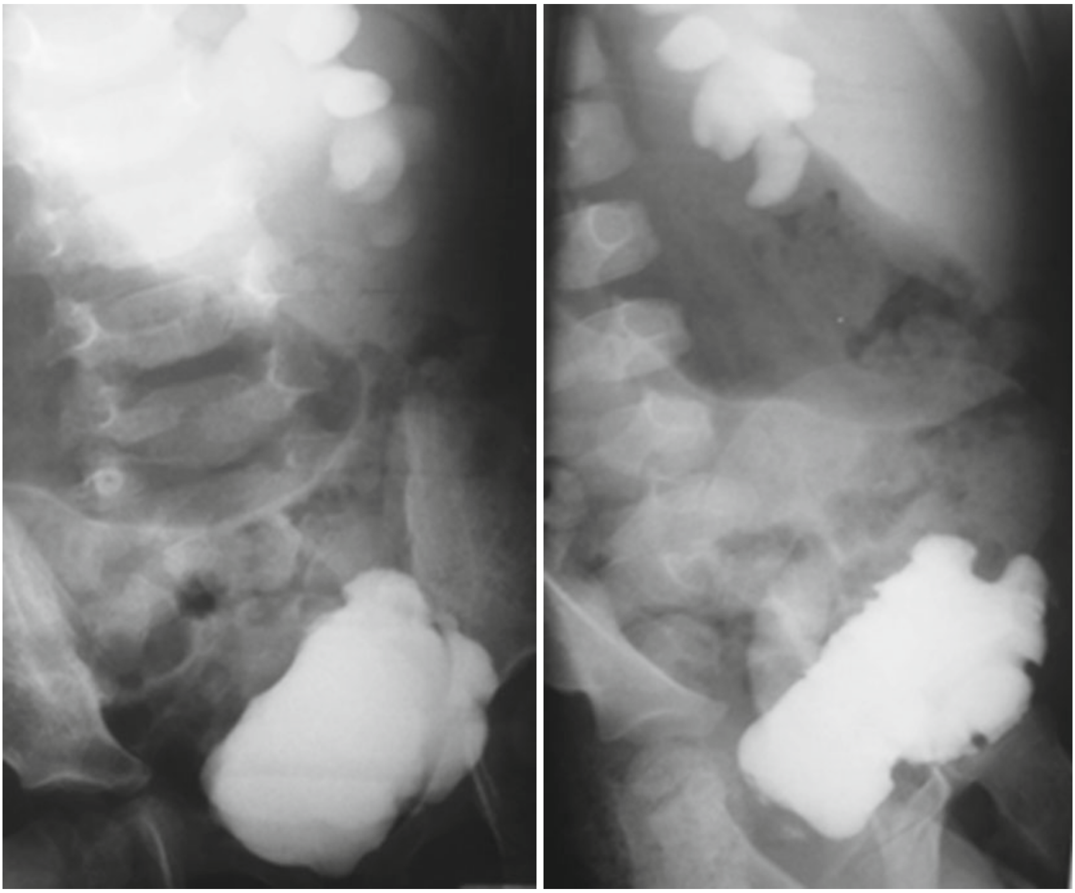


Figs. 8.30 and 8.31 A micturating cystourethrogram showing grade V VUR. Note the dilated tortuous ureters

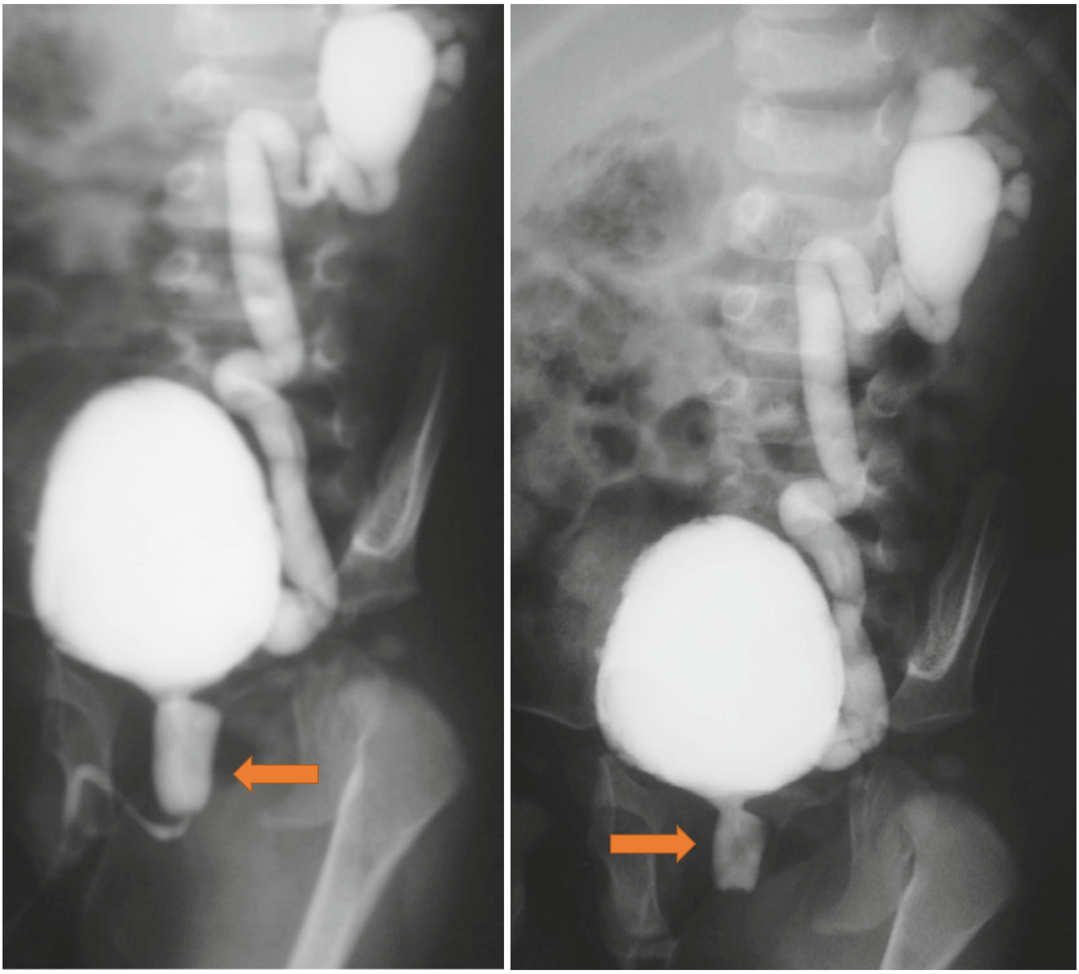
Etiology of VUR

- Primary causes of VUR:
  - Short or absent intravesical ureter
  - Absence of adequate detrusor backing
  - Lateral displacement of the ureteral orifice
  - Paraureteral (Hutch) diverticulum
- Secondary causes of VUR:
  - Cystitis or UTI
  - Bladder outlet obstruction (Posterior urethral valve, urethral stricture, meatal stenosis)
  - Neurogenic bladder
  - Detrusor instability

- Clinical signs and symptoms associated with a febrile UTI in a neonate may include:
  - Irritability
  - Persistent high fever
  - Listlessness
  - Infection in infants can manifest as failure to thrive, with or without fever.
  - Other features include vomiting, diarrhea, anorexia, and lethargy
- In cases of VUR and febrile UTI associated with a serious underlying urinary tract abnormality, the neonate could present with respiratory distress, failure to thrive, renal failure, flank masses, and urinary ascites.

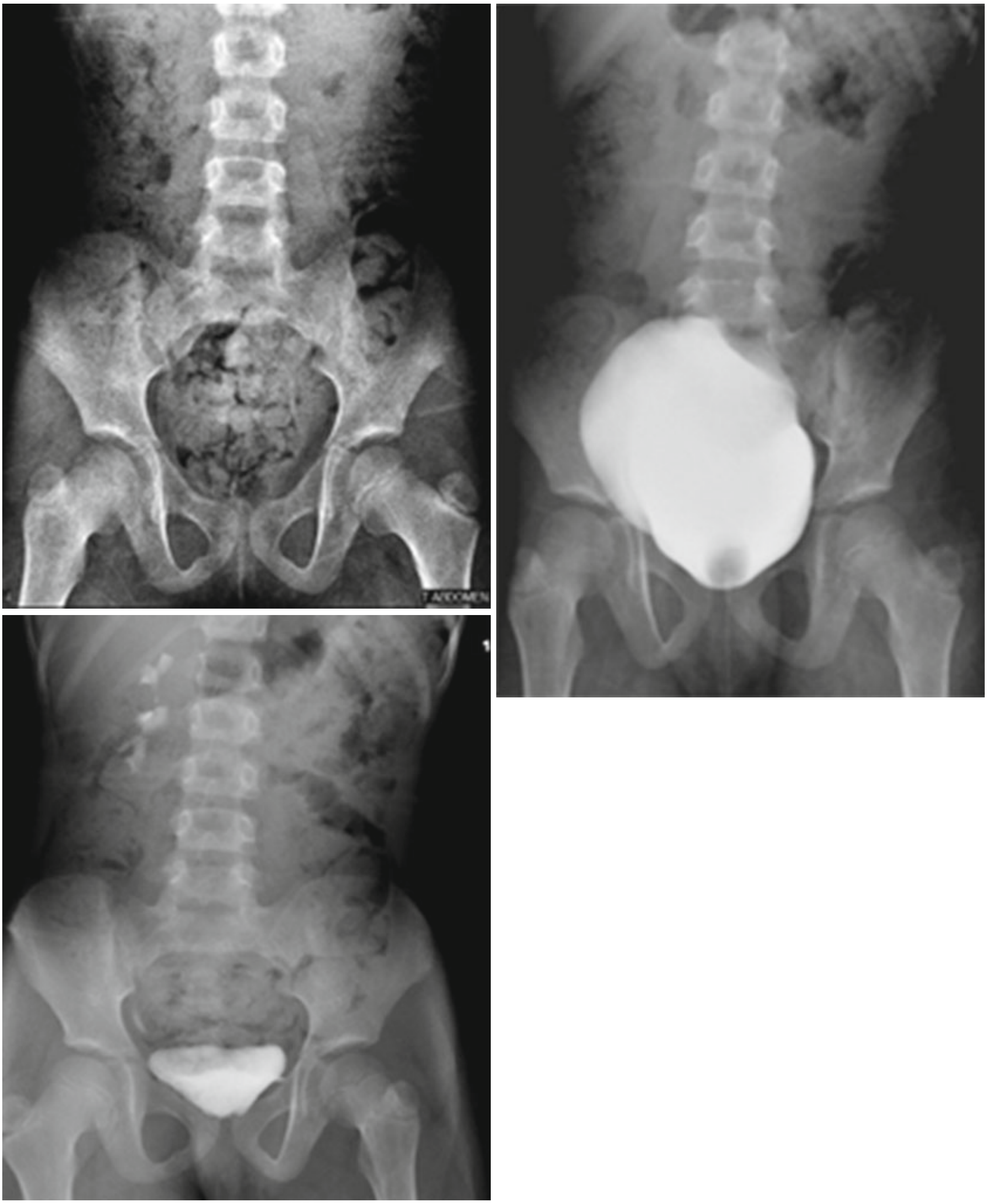


Figs. 8.32 and 8.33 Micturating cystourethrograms showing neurogenic bladder with VUR



Figs. 8.34 and 8.35 Micturating cystourethrograms showing posterior urethral valve and severe right vesicoureteral reflux. Note the dilated posterior urethra

- Older children with VUR and UTI may present with:
  - Nonspecific signs and symptoms
  - Urgency
  - Frequency
  - Dysuria
  - Abdominal pain
  - Incontinence
  - Unless the UTI is associated with a fever, there is little reason to suspect VUR.
  - Sometimes an enlarged urinary bladder may be palpable (Fig. 8.39).
  - A palpable kidney is sometimes seen in those with associated hydronephrosis. Usually the affected kidney is not palpable and small in size as measured by ultrasound.
  - Children occasionally present with advanced reflux nephropathy, manifesting as headaches or congestive heart failure from untreated hypertension, or with uremic symptoms from renal failure.
  - A small group of children without evidence of UTI present with symptoms of sterile reflux, which can include flank or abdominal pain before or during voiding, as well as double voiding or incomplete emptying resulting from delayed drainage of urine out of the upper tracts.



Figs. 8.36, 8.37, and 8.38 Plain abdominal radiograph and micturating cystourethrogram showing bowel dysfunction with chronic constipation and VUR

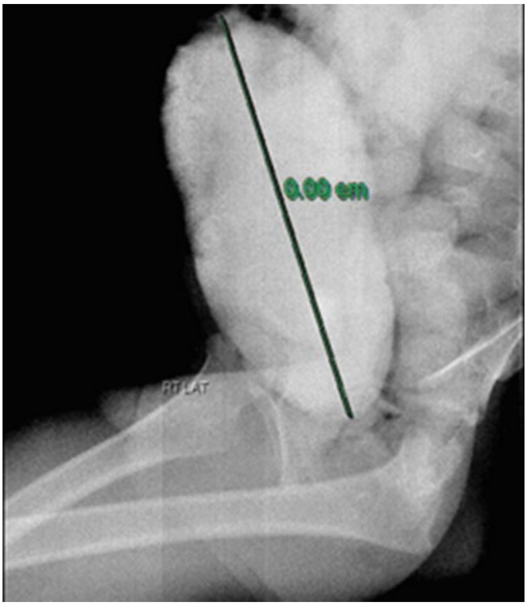
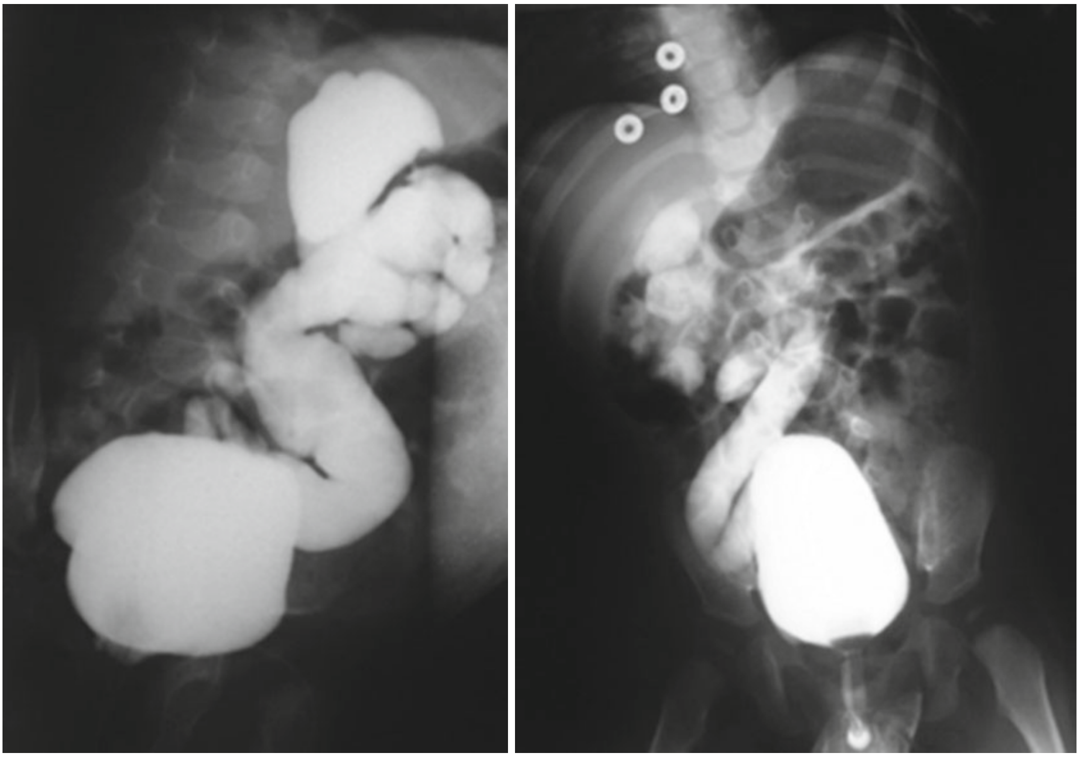


Fig. 8.39 A micturating cystourethrogram showing grade V VUR. Note also the enlarged urinary bladder

8.6 Investigations

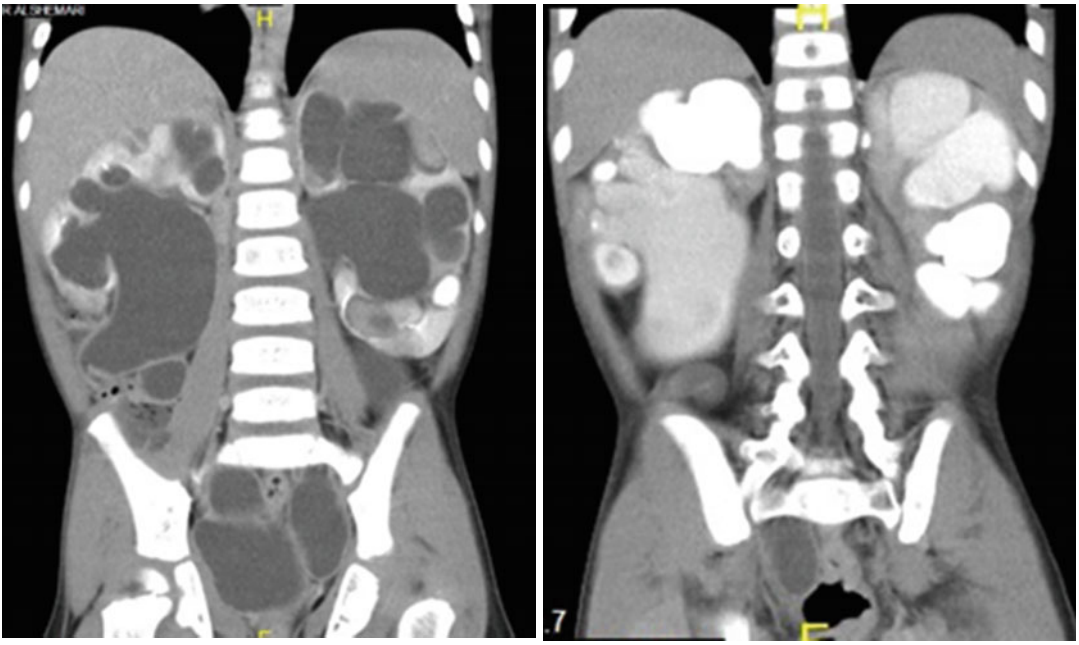
- VUR not only increases the frequency of UTI's, but also the risk of damage to upper urinary structures.
- Vesicoureteral reflux can result in substantial morbidity, both from acute infection and from the sequelae of reflux nephropathy.
- Early diagnosis and treatment of VUR is crucial to avoid permanent renal cortical scarring and subsequent renal insufficiency.
- CBC
- ESR and C-reactive protein
- BUN, serum electrolytes and creatinine
- The diagnosis of UTI depends on urine analysis and urine culture.
- The 2011 American Academy of Pediatrics (AAP) guidelines specify that both a urinalysis showing pyuria and a culture growing more than 50,000 CFU/mL should be the basis for a diagnosis of UTI.
- To diagnose UTI, it is important to obtain a non-contaminated urine specimen.
  - A clean-catch midstream urine specimen is the most acceptable method especially in children who are toilet trained.
  - Growth of more than 100,000 CFU/mL is a significant finding on a midstream-voided specimen.
  - Suprapubic urine aspiration is used in infants and children.
  - Any growth in suprapubic urine sample should be considered significant.
  - Urethral catheterization is an alternative way to obtain a clean urine sample but it is more invasive.
  - Growth of more than 1,000 colony-forming units (CFU)/mL is considered significant in a urine sample obtained by urethral catheterization.
  - The least reliable method is the most common method of obtaining a urine specimen in babies. A urine sample is obtained from a urine collection bag. This method is not reliable and should be discouraged.
  - This method is more useful if there is no growth in the urine sample as false-negative results are unlikely.
  - As many as 10% of urine specimens obtained by this method grow more than 50,000 CFU/mL with no correlation to actual presence of infection.
- Imaging studies are the basis of diagnosis and management of VUR.
- The standard imaging tests include renal and bladder ultrasonography and voiding cystourethrography (VCUG) (Figs. 8.40 and 8.41).
- Indications for imaging studies are as follows:
  - After the first UTI in all children younger than 5 years
  - Children of any age with febrile UTI
  - Boys of any age with UTI
  - Children with prenatally diagnosed hydronephrosis should be evaluated postnatally.
  - Ultrasonography should be performed after the first 3 days of life.
  - Ultrasonography performed during the first 3 days of life may have a high rate of false-negative results because of relative dehydration during the neonatal period.
- The following radiological investigations can be performed to evaluate for VUR:
- Ultrasonography
- VCUG or radionuclide cystography (RNC)



Figs. 8.40 and 8.41 Micturating cystourethrograms showing severe VUR

- Some advocate that children with a history of febrile UTI undergo a dimercaptosuccinic acid (DMSA) renal scan, to assess for evidence of kidney involvement, kidney scarring, or both; if DMSA scan findings are positive, VCUG is recommended.
- Others advocate performing RNC as the initial screening test in girls and then to perform standard VCUG when VUR is observed.
- Other clinicians use VCUG for the initial diagnosis and use RNC for follow-up studies.
- The 2011 American Academy of Pediatrics (AAP) guidelines for management of UTI in children aged 2–24 months recommend that VCUG not be performed after an initial febrile UTI.
- Abdominal ultrasound:
  - The 2011 AAP guidelines recommend that ultrasonography alone should be the initial screening test for children after UTI.
  - The Society for Pediatric Urology continues to recommend that both ultrasonography and cystography be performed.
  - Ultrasonography is not useful to diagnose or rule out VUR.
  - A normal ultrasonography does not exclude vesicoureteral reflux.
  - Ultrasonography is useful to detect upper urinary tract obstruction, to detect dilated ureters and renal scarring.
  - All children with a history of febrile UTI should undergo kidney and bladder ultrasonography.
  - Abdominal ultrasound is usually normal in those with low to moderate VUR.
  - An abdominal ultrasound might suggest the presence of VUR if ureteral dilatation is present.
- Voiding cystourethrography (VCUG):
  - This is the method of choice for diagnosing and grading VUR.
  - VCUG provides precise anatomic detail and allows grading of the reflux.
  - The International Classification System for VUR is as follows:
    - Grade I: Reflux into nondilated ureter

        - Grade II: Reflux into renal pelvis and calyces without dilation
        - Grade III: Reflux with mild to moderate dilation and minimal blunting of fornices
        - Grade IV: Reflux with moderate ureteral tortuosity and dilation of pelvis and calyces
        - Grade V: Reflux with gross dilation of ureter, pelvis, and calyces, loss of papillary impressions, and ureteral tortuosity
    - VCUG should not be performed in the presence of UTI and should be delayed till the child has fully recovered from the UTI. This should be confirmed with a fresh urine analysis and culture.
    - Performance of VCUG during an episode of acute cystitis can result in overestimation of the grade of reflux because of paralysis and laxity of the ureteral musculature by bacterial endotoxin. Conversely, some children demonstrate reflux only during an episode of cystitis.
    - VCUG outlines the urethra in males with posterior urethral valves.
    - VCUG provides information in both boys and girls about bladder capacity and emptying and may reveal signs of outlet obstruction, such as bladder trabeculae or diverticula.
    - Standard VCUG is recommended as the initial study in boys.
- Radionuclide cystography:
    - This is performed by instillation of technetium-99m pertechnetate into the bladder and observation with a gamma camera.
    - This is a highly sensitive test to diagnose VUR.
    - The disadvantage of this investigation is the poor anatomical detail and failure to precisely classify the degree of VUR.
    - Grade I reflux is poorly detected by this study, because the distal ureters are commonly obscured by the bladder
    - Grading of VUR by nuclear cystography is limited to mild, moderate, and severe grades.
    - Many clinicians use VCUG for the initial diagnosis and use RNC for follow-up studies.
- Dimercaptosuccinic acid (DMSA) renal scan:
    - Although the traditional approach in children with UTI has been evaluation for vesicoureteral reflux with VCUG or radionuclide cystography (RNC), some authorities are now advocating a "top-down" approach for children with UTI.
    - In this approach, a child with a history of febrile UTI undergoes a dimercaptosuccinic acid (DMSA) renal scan to assess for evidence of kidney involvement, kidney scarring, or both.
    - Negative DMSA scan findings suggest that clinically significant vesicoureteral reflux is unlikely, obviating the need for VCUG.
    - However, if DMSA scan findings are positive, VCUG is recommended.
    - Reflux grade was significantly associated with the prevalence of renal scarring.
    - VCUG is recommended after the first acute episode of infection is confirmed using dimercapto-succinic acid scintigraphy.
    - Areas of acute inflammation or scarring do not take up the radiopharmaceutical and are revealed as cold spots on imaging.
    - DMSA is used to identify and monitor progression of renal scarring.
    - Patients who are medically treated and develop new or progressive scarring are often considered candidates for surgical correction of vesicoureteral reflux.
    - DMSA can also be used as a diagnostic tool during suspected episodes of acute pyelonephritis but this role is not well defined.
- Urodynamic studies (Cystometrography):
    - These reveal functional abnormalities of the lower urinary tract.
    - These studies are however difficult to perform in infants and small children.
    - Urodynamic studies are important in patients with secondary VUR, such as patients with spina bifida, detrusor instability or boys whose VCUG is suggestive of residual posterior urethral valves.
    - Antireflux surgery is much less successful in patients with secondary reflux, and because of this it is important to identifying



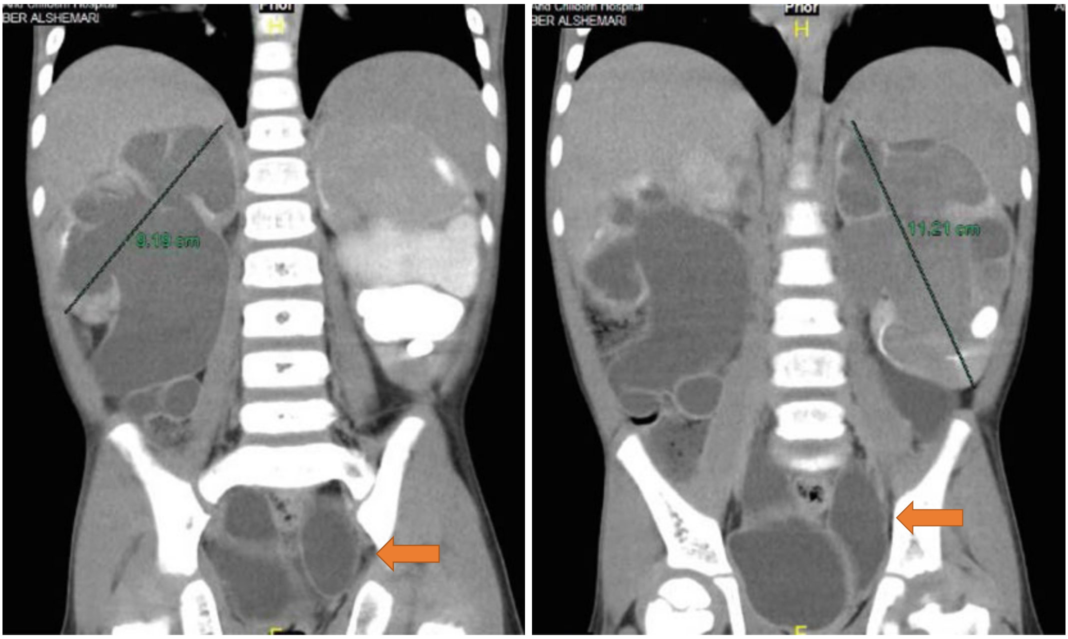
Figs. 8.42 and 8.43 Abdominal CT-scan showing sever hydronephrosis secondary to VUR

such patients before proceeding with operative correction of VUR.

- The cystometrography gives useful information about:
  - Bladder capacity and leak point
  - Pressures at various stages of filling
  - The presence and frequency of uninhibited (involuntary) bladder contractions and compliance.
- Abdominal and pelvic CT-scan and MRU (Figs. 8.42, 8.43, 8.44, 8.45, 8.46, and 8.47):
  - These are useful in delineating:
    - The anatomy and cause as well as the degree of ureteric dilatation
    - Hydronephrosis
    - Renal parenchymal thickness

8.7 Management

- VUR is known to be associated with morbidity and sometimes mortality.
- The management of VUR depends on several factors including:
  - The grade of VUR
  - The compliance of patients with medications and follow-up
  - The presence or absence of urinary tract infections and the frequency of urinary tract infections.
  - The presence of renal scarring
- The aims of treatment are:
  - To prevent episodes of acute pyelonephritis
  - To prevent scarring of the kidney associated with VUR (reflux nephropathy), which increases the risk of hypertension and renal failure
- Although medical conservative treatment of VUR is well established, controversy continues regarding the timing, surgical technique, and benefits.
- Three approaches are used to treat children with vesicoureteral reflux (VUR):
  - Surveillance (observation)
  - Medical treatment
  - Surgical treatment
- The first goal of treatment is to prevent or minimize urinary tract infection.
- Medical management is recommended in children with Grade I-III VUR as most cases will resolve spontaneously.
- This is primarily done by prophylactic antibiotics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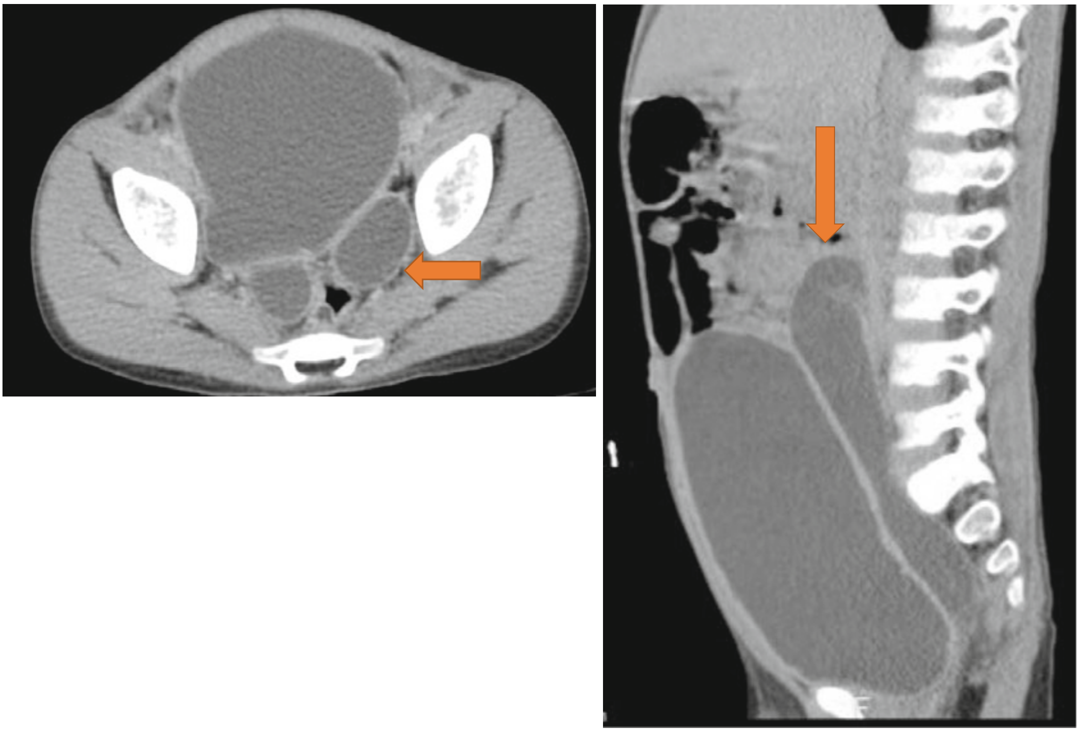
Figs. 8.44 and 8.45 Abdominal CT-scan showing sever hydronephrosis secondary to VUR. Note the dilated ureters and urinary bladder. Note the associated duplex kidneys



Figs. 8.46 and 8.47 Abdominal CT-scan showing severely dilated ureters secondary to VUR. Note the dilated ureters and urinary bladder

- An important aspect of conservative management is bowel and bladder management.
- Children who hold their bladder or who are constipated have a greater number of infections than children who void on a regular schedule.
- Failure of medical treatment to prevent recurrent urinary tract infections, or if the kidneys show progressive renal scarring are indications for surgical interventions.
- A trial of medical treatment is indicated in patients with Grade IV VUR especially younger patients or those with unilateral VUR.
- Patients with Grade V VUR are treated surgically except infants who are treated medically before surgery is indicated.

8.7.1 Medical Treatment of VUR

- This is based on the fact that low-grade VUR resolve spontaneously and sterile reflux does not damage the kidney.
- Medical treatment with prophylactic antibiotics remains the mainstay of initial management of vesicoureteral reflux.
- Because vesicoureteral reflux spontaneously resolves in most children, medical management allows this natural history to take its course while providing some measure of protection against recurrent UTI and renal injury.
- The International Reflux Study has found that children can be managed nonsurgically with little risk of new or increased renal scarring, provided they are maintained infection free.
- The chance of spontaneous resolution of reflux is high in children younger than 5 years with grades I-III reflux and in children younger than 1 year (especially boys).
- Even higher grades of reflux (grades IV–V) may resolve spontaneously as long as the child remains infection free.
- Antibiotic prophylaxis:
  - The recommendations for antibiotic prophylaxis vary according to the presence or absence of renal scarring at diagnosis, and the age at diagnosis.
  - For children without renal scarring at diagnosis, recommendations are as follows:
    - Diagnosis made in infancy:
      - All patients diagnosed at infancy (i.e. <1 year) with grades I–V reflux should be treated initially with continuous prophylactic antibiotics.
    - Diagnosis made in children aged 1–5 years:
      - When unilateral and/or bilateral grades I–IV reflux or unilateral grades III–V reflux are diagnosed in children aged 1–5 years, they should be treated initially with continuous prophylactic antibiotics.
    - Diagnosis made in children aged 6–10 years:
      - Children diagnosed at age 6–10 years with unilateral and/or bilateral grades I–II reflux and unilateral grades III–IV reflux should be treated initially with continuous antibiotic prophylaxis.
      - However, some experts advocate withholding treatment in patients with grade I or II VUR, as most of these patients are at low risk for UTIs and pyelonephritis provided they have no voiding dysfunction or constipation.
  - For children with renal scarring at diagnosis, recommendations are as follows:
    - Diagnosis made in infancy:
      - Infants (i.e. <1 year) with grades I–V reflux should be treated initially with continuous antibiotic prophylaxis.
    - Diagnosis made in children aged 1–5 years:
      - Antibiotic prophylaxis is the preferred option for preschool-aged children (i.e., 1–5 years) with renal scarring at diagnosis, unilateral and/or bilateral grades I–II reflux, unilateral grades III–IV reflux, and bilateral grades III–IV reflux.

    - Diagnosis made in children aged 6–10 years:
        - In children diagnosed at age 6–10 years with renal scarring and unilateral and/or bilateral grades I–II reflux or unilateral grades III–IV reflux, antibiotic therapy is the preferred treatment option.
- The initial treatment of the child with a UTI involves:
    - Supportive care
    - Prompt administration of appropriate antibiotics
    - Timely institution of antibiotic therapy has been shown to be critical in preventing scar formation in kidneys with pyelonephritis. A high index of suspicion for UTI in children is important.
- Since a substantial number of children experience spontaneous resolution of VUR, medical treatment spares this group the morbidity of surgery while protecting the kidneys from further damage.
- Prophylaxis should be started once a child has completed treatment of the initial UTI and continues at least until imaging reveals vesicoureteral reflux.
    - If no vesicoureteral is seen, prophylaxis is discontinued.
    - If vesicoureteral reflux is present, prophylactic antibiotics are continued until:
        - Vesicoureteral reflux resolves
        - Vesicoureteral reflux is surgically corrected
        - The child grows old enough that prophylaxis is deemed no longer necessary.
- Virtually all children with a new diagnosis of grade I–IV reflux, and some with grade V, are given a trial of medical treatment.
- This consists of:
    - Antibiotics given at one fourth of the therapeutic dosage
    - Regular follow-up care and imaging.
    - Regular follow-up consists of renal ultrasonography and VCUG or nuclear cystography every 12–18 months.
    - Regular follow-up and compliance with prophylactic antibiotics are important to avoid the complications of VUR.
    - Once follow-up imaging demonstrates resolution of vesicoureteral reflux, antibiotics are discontinued.
    - Incomplete bladder emptying and constipation are important etiological factors.
    - The importance of aggressive bladder and bowel management for dysfunctional elimination cannot be overemphasized.
    - These patients benefit from bladder training and sometimes the use of anticholinergic medications.
    - Constipation should be avoided and children with primary bowel elimination problem should be treated with enemas, dietary changes, and stool bulking agents.
- In 2014, the results of the Randomized Intervention for children with Vesicoureteral Reflux (RIVUR) study showed that antibiotic prophylaxis with trimethoprim-sulfamethoxazole was associated with a decrease of approximately 50 % in the incidence of recurrent UTI among children with VUR, in comparison with placebo.
- Children on medical management of vesicoureteral reflux are regularly seen on an outpatient basis.
- Routine evaluation includes:
    - Urinalysis and urine culture
    - Appropriate imaging, and blood pressure measurement.
    - Parents can be taught how to perform urinalysis at home and report positive home urinalysis.
    - Parents should be aware of UTI and seek medical care.
- Spontaneous resolution rates decrease as patient age increases and with higher grades of reflux.
- Surgical intervention is recommended for children with reflux that has persisted for more than 3 years with no improvement in the grade of reflux if it is grade II or greater.

8.7.2 Antibiotics Used for Prophylaxis

- Conservative, nonsurgical management is appropriate for mild-to-moderate VUR (grades I–IV) in the absence of breakthrough infections or anatomic abnormalities.
- Antibacterial prophylaxis decreases the incidence of pyelonephritis and subsequent renal scarring with its long term effects for low-to-moderate grades of VUR.
- Long-term antibiotic prophylaxis however, was not shown to be beneficial in those with repeated urinary tract infections.
- In fact, in these patients prophylactic antibiotics will lead to increased risk of bacterial resistance to commonly used antibiotics.
- Trimethoprim-sulfamethoxazole (Bactrim, Bactrim DS, Septra, Septra DS) is an effective antibiotic used to treat uncomplicated UTIs and prevent recurrent infections. It is commonly used as an antibiotic prophylaxis.
- In children, it is given orally as a single dose of 2 mg/kg/day for long term prophylaxis.
- In children <3 months, amoxicillin is preferred.
- Amoxicillin (Amoxil, Biomox, Trimox) is an effective antibiotic for treatment of uncomplicated or recurrent cystitis and also may be used as a long-term prophylaxis to prevent recurrent cystitis.
- In children, amoxicillin is given orally as a single dose of 10 mg/kg/day for long term prophylaxis.
- Nitrofurantoin (Furadantin, Macrobid, Macrodantin) is an antibiotic used specifically for uncomplicated lower UTIs.
- It is given for children >3 months for long term prophylaxis.
- In children >3 months, Nitrofurantoin is given orally as a single dose of 1–2 mg/kg/day.
- Double-suppressive regimens of TMP-SMX every morning and nitrofurantoin every evening may be effective when single-agent prophylaxis fails.

Prophylaxis for pediatric UTIs

Drug	Dosage
TMP-SMX	2 mg/kg/dose once daily or
	5 mg/kg/dose twice per week
Nitrofurantoin	1–2 mg/kg/dose once daily
Ampicillin	20 mg/kg/dose once daily
Amoxicillin	10 mg/kg/dose once daily
Cephalexin	10 mg/kg/dose once daily

8.7.3 Anticholinergics

- One of the secondary causes of VUR is detrusor over activity.
- These patients may benefit from anticholinergics
- These are bladder relaxant medications that control detrusor over activity.
- Oxybutynin (Ditropan):
  - It inhibits action of acetylcholine on smooth muscle and has direct antispasmodic effect on smooth muscles, which in turn cause bladder capacity to increase and uninhibited contractions to decrease.
  - Oxybutynin is given orally to children in a dose of 1–5 mg bid/tid.
- Tolterodine tartrate (Detrol, Detrol LA):
  - It is a competitive muscarinic receptor antagonist for overactive bladder.
  - It has selectivity for urinary bladder over salivary glands.
  - It exhibits a high specificity for muscarinic receptors and has minimal activity or affinity for other neurotransmitter receptors and other potential targets, such as calcium channels.
  - In adults, the dose of Detrol is 1–2 mg PO bid.
- Other important measures to control dysfunctional elimination:
  - It is important to ensure that the child empties his/her bladder completely at regular intervals (every 3 h)
  - Adequate oral hydration
  - Treatment and prevention of constipation

- In children with dysfunctional voiding due to Hinman syndrome, it is important to ensure:
  - Timed voiding with or without biofeedback
  - A regular bowel regimen
  - Intermittent catheterization

8.7.4 Surveillance

- In general, low-grade reflux (grades I–II) have high rates of spontaneous resolution, usually more than 80 %.
- High-grade reflux, especially grade V, is much less likely to resolve.
- Surveillance is infrequently used among those with high-grade VUR.
- Surveillance is still frequently used among older children with VUR, especially boys who have never had a UTI.
- Children with low-grade VUR, especially those who have never had UTI, are sometimes followed on surveillance without antibiotic prophylaxis.

8.8 Surgical Therapy of VUR

8.8.1 Indications for Surgical Interventions

- Absolute indications for surgical interventions include:
  - Breakthrough pyelonephritis
  - Progressive renal scarring in patients receiving antibiotic prophylaxis
  - An associated ureterovesical junction abnormality
- Relative indications for surgical interventions of VUR include:
  - Grades IV and V VUR
  - Persistent VUR despite medical prophylaxis (beyond 3 years)
  - Breakthrough UTIs in patient who are receiving antibiotic prophylaxis
  - Lack of renal growth
  - Multiple drug allergies that preclude the use of prophylaxis
  - A desire to terminate antibiotic prophylaxis (either by the physician or the patient/parents)
  - Medical noncompliance

8.8.2 Indications for Surgical Interventions Based on Age at Diagnosis and the Presence or Absence of Renal Lesions

Children without renal lesions at diagnosis:

- In patients diagnosed with VUR in infancy (<1 year):
  - Surgical repair may be recommended in patients with persistent unilateral grades IV–V reflux or bilateral grades III–V reflux after a period of antibiotic therapy should the parents prefer definitive therapy over watchful management plus antibiotic prophylaxis.
- In children diagnosed at age 1–5 years:
  - Continuous antibiotic prophylaxis is the preferred option as an initial therapy for those with unilateral grade IV reflux; however, surgical repair is a reasonable alternative for grades IV and V reflux.
  - In patients with bilateral grade IV and V reflux, surgical repair is recommended.
  - Surgery is recommended for children with persistent grades III–V reflux who have not remained infection-free with antibiotic therapy.
  - Endoscopic treatment may be recommended in children with grade III–IV who have not shown any improvement in the reflux grade, who do not wish to receive further antibiotics, or who have had UTI.
- In children diagnosed at age 6–10 years:
  - In patients with bilateral grades III–IV reflux, surgical repair is the preferred option, although continuous antibiotic therapy is a reasonable alternative.
  - Patients with grade V reflux should undergo surgical repair.
  - In patients with persistent grades I–II reflux after a period of antibiotic prophylaxis,

    consensus is lacking regarding the role of continued antibiotics versus surgery.
  - Surgery is an option for persistent reflux in children with grades III–IV reflux in whom initial antibiotic therapy has failed; either an open surgical or an endoscopic approach may be used.

Children with renal lesions at diagnosis:

- In patients diagnosed with VUR in infancy (<1 year):
  - In children with grade V reflux and scarring, continuous antibiotic prophylaxis is the preferred option as an initial treatment; primary surgical repair is a reasonable alternative.
  - If the kidney is noted to have poor function (<15 % on DMSA scan) consider removing the kidney and the ureter down to the bladder.
  - Consensus is lacking regarding the role of continued antibiotics versus surgery in patients with persistent grades I–II reflux after a period of antibiotic prophylaxis. These patients may be candidates for endoscopic treatment.
  - In boys with persistent unilateral grades III–IV reflux, surgical repair is the preferred option.
  - Boys with persistent bilateral grades III–IV reflux, girls with persistent unilateral and/or bilateral grades III–IV reflux, and any children with persistent grade V reflux should undergo surgical repair, with an option for endoscopic treatment in grades II–IV.
- In children diagnosed at age 1–5 years:
  - In children with bilateral grades III–IV reflux and renal lesions, antibiotic therapy is the preferred option; however, surgical repair is a reasonable alternative.
  - Patients with unilateral and/or bilateral grade V disease and scarring should undergo surgical repair as initial treatment or nephroureterectomy if the kidney has been shown to have little or no function on DMSA scan.
  - Consensus is lacking regarding the role of continued antibiotics versus surgery for patients with persistent grades I–II reflux after a period of antibiotic prophylaxis.
  - Girls with persistent unilateral and/or bilateral grades III–IV reflux and boys with persistent bilateral grades III–IV reflux should undergo surgical repair, either open or endoscopic.
  - Surgery is also an option for boys with persistent unilateral grades III–IV reflux.
  - For patients with persistent grade V reflux who have not undergone surgery as initial treatment, surgical repair is recommended.
- In children diagnosed at age 6–10 years:
  - Patients diagnosed with bilateral grades III–IV reflux or grade V reflux can undergo surgical repair as initial treatment.
  - Consensus is lacking regarding the role of continued antibiotics versus surgery for patients with persistent grades I–II reflux after a period of prophylaxis.
  - Patients with persistent unilateral grades III–IV reflux who have not undergone surgery as initial treatment should be offered either open surgical repair or endoscopic treatment.
- Surgical therapy options for VUR include:
  - Open surgical procedures
    - Leadbetter-Politano procedure
    - Cohen procedure
  - Endoscopic injection (STING/HIT procedures)
  - Laparoscopic repair
  - Robotic assisted repair

8.8.3 Endoscopic Injection

- The most dramatic change in the treatment of vesicoureteral reflux over the past decade has been the rapid growth in the use of endoscopic treatment.
- Endoscopic treatment of VUR was popularized by Puri and O’Donnell in 1980s.
- Currently, it is the surgical treatment of choice for children with VUR.

- The principle of the procedure is to inject, under cystoscopic guidance, a biocompatible bulking agent underneath the intravesical portion of the ureter in a submucosal location.

Indications for Surgical Treatment of VUR

- Breakthrough febrile UTIs despite adequate antibiotic prophylaxis
- Severe reflux (grade V or bilateral grade IV) that is unlikely to spontaneously resolve, especially if renal scarring is present
- Mild or moderate reflux in females that persists as the patient approaches puberty, despite several years of observation
- Poor compliance with medications or surveillance programs
- Poor renal growth or function or appearance of new scars

- The bulking agent elevates the ureteral orifice and distal ureter in such a way that the lumen is narrowed, preventing regurgitation of urine up the ureter but still allowing its antegrade flow.
- The procedure became popular and has several advantages:
  - It is performed with general anesthesia on an outpatient basis
  - A short surgical time
  - Low surgical morbidity
  - Comparable success rates
  - Preservation of the option for subsequent open surgical repair
  - It can be repeated
  - It can be used to treat different grades of VUR and some authors are using this technique to treat even grade IV and V VUR.
- Some clinicians and because of these advantages are now advocating endoscopic treatment as initial management for newly diagnosed vesicoureteral reflux.
- They argue that immediate antireflux surgery obviates the need for long-term antibiotics and repeated imaging studies.
- This however, inevitably results in the overtreatment of a large number of children because VUR is known to spontaneously resolve in most children, and even those with persistent VUR may not have a clinical indication for antireflux surgery.
- Add to this, the fact that the true long-term success rates for endoscopic treatment are still to be determined.
- Endoscopic injection involves applying a gel around the ureteral opening to create a valve like function which stop urine from flowing back up the ureter.
- Some authors emphasize the importance of creating a large mound or “volcanic” appearance of the bulking agent under the orifice, compressing the orifice into a slit.

Advantages of Endoscopic Treatment of VUR

- It is performed on an outpatient basis
- A short surgical time
- Low surgical morbidity
- Comparable success rates
- Preservation of the option for subsequent open surgical repair
- It can be repeated

- Other authors have described an intramural injection, in which the distal ureter is distended with a jet of saline from the cystoscope, allowing the injection needle to be advanced into the submucosa of the intramural ureter at 6 o’clock.
- The gel consists of two types of sugar-based molecules called dextranomer and hyaluronic acid.
- Trade names for this combination include Deflux and Zuidex.
- Both are biocompatible, which means that they do not cause significant reactions within the body.
- The procedure of endoscopic treatment of VUR:
  - The procedure is performed under general anesthesia and complete aseptic technique.
  - The patient is placed in the lithotomy position.

  - Cystourethroscopy is performed and the bladder and ureteral orifices are inspected.
  - An injection needle is then introduced advanced, bevel up to the ureteral orifice.
  - The orifice is kept open by hydrodistending it with irrigation fluid.
  - The needle is then advanced into the ureter.
  - A submucosal puncture is made and the bulking material is slowly injected.
  - As it spreads in the submucosal space, the material elevates the intravesical ureter, and the orifice acquires an inverted smile appearance.
  - The needle is slowly withdrawn after between 0.5 and 2 mL of material has been injected.
  - A second injection may be carried out at the base of the newly created mound to further elevate the ureteral orifice.
  - The bladder is emptied and reinspected.
  - Any bleeding vessels may be cauterized with a Bugbee electrode.
  - Some authors have described an intramural injection, in which the distal ureter is distended with a jet of saline from the cystoscope, allowing the injection needle to be advanced into the submucosa of the intramural ureter at 6 o'clock.
- In general, the success rates with endoscopic treatment are significantly lower than those reported for open antireflux surgery.
- Most studies of endoscopic treatment have found that success rates are lower for higher grades of vesicoureteral reflux.
- The reported success rate of grade IV VUR was 63 % after one injection.
- Polytetrafluoroethylene (Teflon) was used but concerns over its safety have limited its use.
- Other bulking agents that have been reported include:
  - Autologous fat
  - Blood
  - Chondrocytes
  - Bovine collagen
  - Polydimethylsiloxane
- Concerns over particle migration, carcinogenesis, and technical handling problems have limited their use.
- Children who undergo endoscopic antireflux surgery need continued follow-up.
  - They require post procedure imaging, including voiding cystourethrography (VCUG) at 3–4 months postsurgery.
  - Patients should be maintained on antibiotic prophylaxis until resolution of vesicoureteral reflux is confirmed.
- It is important to note that as many as 25 % of children whose VUR was cured on the initial post endoscopic injection VCUG (3–4 months) subsequently had recurrence of VUR on delayed VCUG (12 months).
- This is attributed to several factors including:
  - Reabsorption of the injected material
  - Migration of the injected material
  - Associated dysfunctional voiding
- It was shown that on long term, DHA implants can strongly resemble a stone in the distal ureter on CT scanning, apparently due to calcification of the DHA implant.
- Persistent vesicoureteral reflux after open antireflux surgery:
  - The initial management is a repeat injection.
  - Many investigators routinely use up to three separate injections.
  - Patients who fail multiple injections should be reevaluated and treated for causes of secondary VUR.
  - Patients with persistent VUR and in the presence of a surgical indications for correction of VUR should have open surgery.

Bulking Agents Used Endoscopically to Treat VUR

- Dextranomer and hyaluronic acid (DHA) (Deflux and Zuidex)
- Polytetrafluoroethylene (Teflon)
- Autologous fat
- Blood
- Chondrocytes
- Bovine collagen
- Polydimethylsiloxane

- The success of endoscopic treatment of VUR are as follows:
    - Grades I and II: 78.5 %
    - Grade III: 72 %
    - Grade IV: 63 %
    - Grade V: 51 %
- Endoscopic treatment of VUR can be repeated up to three times and this increases the overall success rate to 85 %.
- The most common complications following endoscopic treatment of VUR:
    - Transient ureteral obstruction
    - Urinary tract infection
    - The success rates at 1 year are significantly lower than initial success rates

8.8.4 Surgical Management

Surgical Treatment of VUR

- Open antireflux surgery
    - An extravesical approach
        - The Lich-Gregoire repair
        - Extravesical detrusorrhaphy (Hodgson-Zaontz)
    - An intravesical approach
        - The Cohen cross-trigonal technique
        - The Politano-Leadbetter procedure
        - The Glenn-Anderson repair
- Laparoscopic antireflux operation
- Robotic assisted antireflux operation
- Endoscopic antireflux surgery

- The aim of open, laparoscopic and robotic assisted antireflux operations is reconstruction of the ureterovesical junction to create a lengthened submucosal tunnel for the ureter, which functions as a one-way valve preventing backflow of urine into the ureter as the bladder fills.
- There are several surgical techniques to achieve this:
    - Open antireflux surgery
        - An extravesical approach
            - The Lich-Gregoire repair
            - Extravesical detrusorrhaphy (Hodgson-Zaontz)
        - An intravesical approach
            - The Cohen cross-trigonal technique
            - The Politano-Leadbetter procedure
            - The Glenn-Anderson repair
    - Laparoscopic antireflux operation
    - Robotic assisted antireflux operation
    - Endoscopic antireflux surgery
- The accepted indications for surgical treatment of VUR include the following:
    - Breakthrough febrile UTIs despite adequate antibiotic prophylaxis
    - Severe reflux (grade V or bilateral grade IV) that is unlikely to spontaneously resolve, especially if renal scarring is present
    - Mild or moderate reflux in females that persists as the patient approaches puberty, despite several years of observation
    - Poor compliance with medications or surveillance programs
    - Poor renal growth or function or appearance of new scars
- The intravesical approach to correct VUR depends on the followings:
    - Cystoscopy is performed and the bladder and ureteral openings are defined.
    - The bladder is opened anteriorly via a low abdominal incision.
    - The affected ureter or ureters if bilateral VUR is present are dissected and separated from their attachments to the bladder muscle and connective tissue.
    - When enough length of the ureter is separated, the ureter is pulled across the trigone through a submucosal tunnel.
    - The ureteric opening is sutured at the end of the tunnel to create the necessary 5:1 ureter length-to-diameter ratio.
- These are the basic principles of the Cohen cross-trigonal technique to treat VUR.
- This is the most popular intravesical technique used to treat VUR (Fig. 8.48).
- The Politano-Leadbetter procedure:
    - The principle is similar to the Cohen technique
    - The ureter is dissected completely free of its attachments and passed through a new muscular hiatus created higher on the bladder wall.

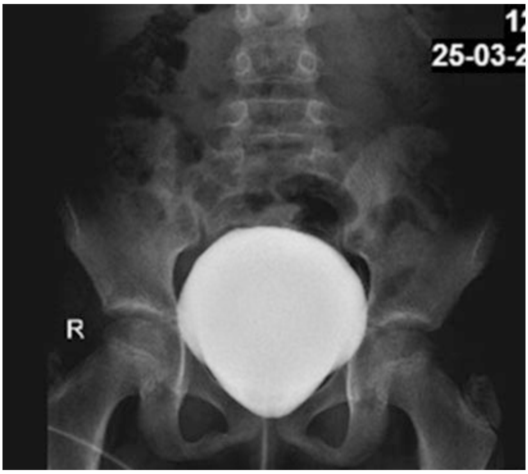


Fig. 8.48 A micturating cystourethrogram showing no VUR after anti-reflux surgery

  - The ureter is then passed down through a submucosal tunnel, and the orifice is sutured to the mucosa at its original hiatal position.
- The Glenn-Anderson repair creates a new ureteral hiatus more distal to the original hiatus.
- Extravesical approach:
  - This was developed in an effort to avoid the time and morbidity associated with the cystotomy and ureteral anastomosis required for intravesical repair.
  - It is particularly useful in patients with unilateral reflux.
  - The Lich-Gregoire repair:
    - The bladder is approached via the retroperitoneum.
    - The ureter is dissected from the detrusor muscle, but the orifice is left intact.
    - A narrow furrow in the detrusor muscle is created, down to but not disrupting the mucosa, extending cephalad from the ureteral orifice.
    - The distal ureter is then laid into this furrow and the detrusor closed over it.
- One complication of the extravesical approach is postoperative urinary retention, which generally resolves spontaneously.
- Rare reports of permanent voiding dysfunction and retention in patients undergoing bilateral extravesical procedures have led some surgeons to use this technique only for unilateral VUR.
- Extravesical detrusorrhaphy (Hodgson-Zaontz):
  - Following the initial dissection, the ureter is dissected extravesically down to the ureterovesical junction.
  - The terminal ureter is dissected free from perivesical tissues except its attachment to the bladder mucosa which should remain intact.
  - Electrocautery is used to incise the bladder muscle down to the mucosa for a 5-cm arc around the ureterovesical junction.
  - The lateral edges of the incision are undermined to create a trough that will form a new bed for the ureter.
  - It is important not to open the mucosa of the bladder.
  - The ureter is then telescoped into the bladder so it courses within a long subepithelial tunnel.
  - Neither a ureteral stent nor a perivesical drain is needed.
  - An indwelling Foley catheter is left overnight.
- Laparoscopic and robotic assisted repair of VUR may be possible alternatives to open ureteral reimplantation.
- Post-operative follow-up:
  - Continue prophylactic antibiotics
  - A postoperative renal ultrasonography in 1–2 months.
  - A nuclear cystography in 3 months
  - Perform interval renal ultrasonography annually for 3 years
  - After confirming resolution of VUR, discontinue antibiotic prophylaxis.
- Complications due to reimplantation of the ureters occur in less than 1 % of cases, and include the followings:
  - Gross hematuria
  - Bleeding in the retroperitoneal space
  - Infections
  - Ureteral obstruction
  - Injury to adjacent organs
  - Persistent reflux
  - Recurrent UTIs despite antireflux surgery
- Gross hematuria:
  - Gross hematuria after ureteral reimplantation is common.

  - Persistent bleeding or clots indicate inadequate hemostasis at the time of operation.
  - Hematuria is often self-limited and does not require operative intervention.
  - Continue prolonged catheterization is important until hematuria resolves.
  - Patients rarely need transurethral fulguration or reoperation.
- Persistent, transient, contralateral reflux:
  - Persistent reflux of the reimplanted ureter and development of de novo reflux of the contralateral side are usually temporary and resolve spontaneously.
  - Transient postoperative reflux is usually caused by detrusor instability of the healing bladder.
  - Persistent reflux of the ipsilateral ureter in the absence of secondary causes (e.g. a poorly compliant bladder) is usually caused by a technical error.
  - Some technical problems associated with ureteral reimplantation include:
    - Inadequate ureteral mobilization
    - Short intramural tunnel
    - Inadequate anchoring of the ureter
    - Inappropriate placement of the ureteral orifice
  - These technical errors are treated by reoperation or endoscopic injection if the reflux is grade III or less.
  - Most contralateral reflux is caused by recurrent or previously undiagnosed reflux.
  - Contralateral reflux may become evident when the contralateral refluxing ureter is no longer refluxing. These can managed conservatively, and usually subside spontaneously.
  - If a patient experiences persistent or severe VUR following repair, perform a thorough workup, including urodynamics, imaging, and cystoscopy.
- Postsurgical obstruction after open antireflux surgery:
  - Most cases of postoperative upper tract obstruction are mild, produce no symptoms, and spontaneously resolve.
  - These cases are due to:
    - Edema at the ureteroneocystostomy site
    - Intraureteral blood clots
    - Intraureteral mucous
    - Bladder spasms
    - Submucosal bladder hematoma
  - Rarely, the obstruction is severe and present late, 1–2 weeks postoperatively.
  - This is usually secondary to ischemia of the distal reimplanted segment of the ureter leading to fibrosis and stricture, an incorrect tunnel construction or too tight ureteral hiatus.
  - These patients present with flank or abdominal pain, nausea, and vomiting.
  - Obtain a renal ultrasonography, intravenous pyelography, or nuclear renography to confirm diagnosis.
  - Ultrasonography can be difficult to assess in patients who had significant dilation preoperatively.
  - Rarely, the obstruction is intermittent due to kinking or angulation of the reimplanted ureter with bladder filling.
  - Most postoperative ureteral obstructions resolve spontaneously; however, temporary ureteral stenting may be necessary.
  - Cystoscopy, ureteroscopic dilation and stent placement may correct mild obstruction or stenosis.
  - Percutaneous placement of a nephrostomy tune may be necessary if a transvesical approach is not achievable.
  - Treatment for high-grade obstruction is surgical revision of the obstructed system.

8.9 Mortality/Morbidity

- Modern series consistently report success rates greater than 95 % for antireflux surgery.
- In cases in which reflux persists postoperatively, initial observation with continued antibiotic prophylaxis is indicated.
- A substantial number of patients with reflux at the first postoperative study have complete resolution at the 1-year follow-up point.
- Reoperation is generally reserved for patients with persisted febrile UTI despite prophylaxis.

- A very high percentage of patients in whom surgery has failed have voiding dysfunction, thus urodynamic evaluation should be considered in these patients, especially if reoperation is considered.
- New contralateral vesicoureteral reflux after unilateral antireflux surgery:
  - New onset of vesicoureteral reflux in a renal unit that had no vesicoureteral reflux on preoperative imaging occurs in 10–32 % of patients after open correction and 7–14 % of patients after endoscopic correction.
  - In general, the new vesicoureteral reflux is usually of low grade and more likely to spontaneously resolve.
- Outcome and morbidity of VUR:
  - The success rate of ureteral reimplantation is higher than 95 %.
  - The success rate of endoscopic treatment is lower than open surgical treatment but offers an alternative to either medical treatment or open surgical treatment.
  - Following surgical repair, the incidence of pyelonephritis significantly decreases in comparison to medical management with long-term antibiotic therapy.
  - The incidence of cystitis or renal scarring is the same following both medical and surgical management of VUR.
- Morbidity associated with vesicoureteral reflux:
  - Acute urinary tract infection
  - Reflux nephropathy
  - Changes in renal function:
    - Decrease in urine-concentrating ability
    - Decrease in glomerular filtration rate
  - Decreased renal and somatic growth
  - Hypertension
    - Reflux nephropathy may be the most common cause of childhood hypertension.
    - This is secondary to elevated renin levels produced by scarred renal tissue
    - The presence of hypertension correlates well with the degree of renal scarring.
  - Renal failure
    - The most devastating outcome of reflux nephropathy is renal failure.
    - It is estimated that 15–30 % of renal failure in children and young adults is attributed to chronic pyelonephritis and reflux nephropathy.
    - Although renal failure is a devastating complication of vesicoureteral reflux, it actually affects only a small minority of children with VUR.

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Pediatric Urolithiasis

9

9.1 Introduction

- Urolithiasis (from Greek *oûron*, “urine”, + *lithos*, “stone”, + *-iasis*) are calculi formed or located anywhere in the urinary system.
- It comprises:
  - Nephrolithiasis (the formation of kidney stones)
  - Ureterolithiasis (the formation of stones in the ureters)
  - Cystolithiasis (the formation of bladder stones)
- Nephrocalcinosis refers to increased calcium content in the parenchyma of the kidney.
- Urolithiasis is a fairly common disease in adults with an estimated prevalence of 3–5 %.
- Urolithiasis has been regarded as an uncommon condition in children.
- Childhood urolithiasis however, is an increasingly recognized condition.
- The estimated incidence in the United States from the 1950s to the 1970s is approximately 1–2 % that of adults. More recent studies from the United States suggest an increase in the incidence and prevalence of childhood urolithiasis, with one study demonstrating a nearly fivefold increase in the incidence in the last decade.
- Calculi are particularly uncommon in children of African descent.
- In certain regions, such as Southeast Asia, the Middle East, India, and Pakistan, calculi are endemic.
- The endemic calculi observed in developing nations are often confined to the bladder and comprise predominantly ammonium acid, urate, and uric acid, and seem to correlate with a decreased availability of dietary phosphates.
- Most calculi in the United States are found in the kidneys or ureters. They are composed of either calcium oxalate or calcium phosphate, and often associated with a metabolic abnormality.
- The exact incidence of urolithiasis in childhood is not known but it is believed to be approximately 10 % of that in adults, which is around 5 % in developed countries.
- Urolithiasis in childhood differs substantially from that in adults with regard to:
  - Etiology
  - Clinical features
  - Diagnostic techniques
  - Treatment.
- Approximately 40 % of children with urolithiasis have a positive family history of kidney stones.
- Most of the children with urolithiasis have an underlying metabolic etiology.
- Materials that produce stones in the urinary tract of children include the following:
  - Calcium with phosphate or oxalate
  - Purine derivatives
  - Magnesium ammonium phosphate (struvite)
  - Cysteine

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A.H. Al-Salem, *An Illustrated Guide to Pediatric Urology*, DOI 10.1007/978-3-319-44182-5_9

  - Combinations of the above items
  - Drugs or their metabolites (e.g., phenytoin, triamterene)
  - Melamine-contaminated milk powder consumption

9.2 Etiology

- The development of urinary stones depends on the following three factors:
  - Supersaturation of stone-forming components in urine
  - The presence of chemical or physical stimuli in urine that promote stone formation
  - Inadequate amount of chemicals in urine that inhibit stone formation (e.g., magnesium, citrate)
- The followings are contributing factors to urinary stones developments:
  - Dietary factors
  - A high oxalate intake may contribute to calcium oxalate stone production.
  - Excessive purine intake may contribute to the production of stones containing uric acid and uric acid plus calcium stones.
  - A ketogenic diet, prescribed to reduce seizures, places children at risk for both uric acid and calcium stone formation.
- The development of calcium urolithiasis is attributed to by increased urinary calcium.
- Urinary calcium increases:
  - With increased dietary calcium intake.
  - With increased sodium chloride intake.
  - Severe dietary phosphate restriction increases urine calcium excretion.
  - A diet high in protein from animal sources, glucose or sucrose increases urinary calcium.
  - Vitamins A and D can contribute to calcium urolithiasis when taken in excessive amounts.
  - Fructose consumption is also associated with an increased risk of kidney stones.
- Drugs taken by the patients may contribute to the development of urolithiasis for the following reasons:
  - The drug or its metabolites may precipitate as stones (e.g., phenytoin, triamterene, sulfadiazine, felbamate, ceftriaxone).
  - The drug may increase the concentration of stone-forming minerals by increasing the filtered load or decreasing the tubular reabsorption.
    - Anticancer agents increase the filtered load of uric acid.
    - Glucocorticoids increase the filtered load of calcium.
    - Allopurinol increases the filtered load of xanthine in patients with tumor lysis to produce xanthinuria.
    - Furosemide decreases tubular calcium reabsorption, leading to increased urine calcium concentration.
  - The drug may alter urine pH, decreasing the solubility of a stone-forming agent.
    - In children with distal renal tubular acidosis, bicarbonate probably contributes to stone formation by further alkalinizing the urine.
- Fluid intake quantitatively and qualitatively is an important factor for the development of urolithiasis.
  - A low fluid intake leads to concentrated urine and increases the risk of stone formation.
  - Water may have a high mineral content in some areas.
  - Milk contains significant calcium and vitamin D.
  - Orange juice may be supplemented with calcium.
  - Tea contains oxalate and often sucrose.
  - Many drinks (e.g., sports drinks) contain sodium chloride and sucrose.
- Several diseases, or the medications used to treat them, increase the risk of urolithiasis development. These include:
  - Distal renal tubular acidosis
  - Short-bowel syndrome
  - Inflammatory bowel disease
  - Intractable seizures
  - Cystic fibrosis
- Urolithiasis is also a known complication following renal transplant for the following reasons:
  - Retention of suture material
  - Recurrent urinary tract infection
  - Hypercalciuria
  - Urinary stasis

- Gastrostomy tube–fed children are at higher risk of urolithiasis for the following reasons:
  - The concomitant use of Topiramate (an anticonvulsant)
  - Urinary tract infection
  - Subclinical chronic dehydration
- Risk factors for pediatric urolithiasis include the following:
  - Habitually low urine volume
  - High urine excretion of calcium
  - High urine excretion of uric acid
  - High urine excretion of oxalate
  - Low urine pH: Uric acid and cysteine are less soluble in acid urine.
  - High urine pH: Struvite and calcium phosphate are less soluble in alkaline urine.
  - Nidus for crystal precipitation
- In children, hypercalciuria is a significant risk factors for urolithiasis.
- Other risk factors for urolithiasis include:
  - Developmental abnormalities of the urinary tract
  - Urinary obstruction
  - Urinary stasis
  - Urinary tract infection with urea-splitting microorganisms
- Functional or anatomic obstruction predisposes children to stone formation by promoting stasis of urine and infection.
- Only 1–5 % of children with urologic abnormalities develop calculi, suggesting a concomitant metabolic abnormality in patients with both urologic abnormalities and calculi.
- Although infection is commonly associated with kidney stones, it is unlikely to be causative of non–struvite calculi.
- Genitourinary anomalies are found in approximately 30 % of children with urolithiasis. These include:
  - Hydronephrosis
  - Duplex ureter
  - Posterior uretheral valves
  - Bladder exstrophy
- Urolithiasis is associated with an identifiable metabolic abnormality in approximately 40–50 % of children.
- The major metabolic abnormalities associated with urolithiasis include:
  - Hypercalciuria
  - Hyperoxaluria
  - Hypocitraturia
  - Cystinuria
  - Hyperuricosuria
- Hypercalciuria or hypocitraturia are the most frequently reported abnormalities in children.
- In the United States the chemical composition of urolithiasis is as follows:
  - 40–65 % are calcium oxalate
  - 14–30 % are calcium phosphate
  - 10–20 % are struvite (magnesium ammonium phosphate)
  - 5–10 % are cysteine
  - 1–4 % are uric acid
- Rarely, stones may also comprise xanthine, or 2, 8-dihydroxyadenine.
- Metabolic abnormalities known to be associated with increased risk for urolithiasis include:
- Hypercalciuria
  - Hypercalciuria is formally defined as calcium excretion of greater than 4 mg/kg/day in children older than 2 years.
  - Hypercalciuria is found in approximately 30–50 % of children with urolithiasis.
  - The most common cause in children and adults is idiopathic hypercalciuria.
  - Idiopathic hypercalciuria is defined as hypercalciuria that occurs in the absence of hypercalcemia in patients in whom no other cause can be identified.
  - Familial idiopathic hypercalciuria appear to be transmitted in an autosomal dominant fashion with incomplete penetrance.
  - Approximately 4 % of asymptomatic healthy children demonstrate evidence of idiopathic hypercalciuria, and 40–50 % of those children have a positive family history of urolithiasis.
  - In school-aged children, a calcium to creatinine ratio of 0.2 mg/mg or less is considered normal, although higher values are reported in younger children.
  - When hypercalciuria is observed, several conditions must be excluded before establishing a diagnosis of idiopathic hypercalciuria.

  - In children with hypercalcemic hypercalciuria, the following possibilities should be excluded:
    - Hyperparathyroidism
    - Hypervitaminosis D
    - Prolonged immobilization
    - Sarcoidosis
    - Malignancy
    - Juvenile idiopathic arthritis
    - Corticosteroid excess
    - Adrenal insufficiency
    - William syndrome
  - In children with hypocalcemic hypercalciuria, the following possibilities should be excluded:
    - Hypoparathyroidism
    - Autosomal, dominant hypocalcemic hypercalciuria
  - Other causes of hypercalciuria include:
    - Idiopathic hypercalciuria
    - Prematurity
    - Diuretics (furosemide and acetazolamide)
    - Anticonvulsants (topiramate and zonisamide)
    - Ketogenic diet
    - Dent disease
    - Bartter syndrome
    - Familial hypomagnesemia with hypercalciuria and nephrocalcinosis (FHHNC)
    - Distal renal tubular acidosis (dRTA)
    - Hereditary hypophosphatemic rickets with hypercalciuria (HHRH)
    - Medullary sponge kidney
- Dent disease:
  - This is an X-linked inherited condition caused by a mutation in the *CLCN5* gene.
  - The condition is characterized by low-molecular-weight proteinuria, nephrocalcinosis, normocalcemic hypercalciuria, nephrolithiasis, and chronic kidney disease.
- Bartter syndrome:
  - This is an autosomal recessive condition characterized by renal salt wasting, hypokalemia, metabolic alkalosis, hypercalciuria, and normal serum magnesium levels.
  - Children younger than 6 years typically present with salt craving, polyuria, dehydration, emesis, constipation, and failure to thrive.
  - Severe polyhydramnios, prematurity, and occasionally sensorineural deafness are the hallmark features.
  - There are four types of Bartter syndrome deepening on the mutation.
  - Mutations in the *SLC12A, KCNJ1,* and *BSND* genes (Bartter syndrome type I, type II, and type IV, respectively) typically result in severe dysfunction of the thick ascending limb of the loop of Henle in the neonatal period (neonatal Bartter syndrome).
  - Mutations in the *ClCKB* gene (Bartter syndrome type III) usually cause milder dysfunction of the thick ascending limb of the loop of Henle and often present outside the neonatal period (classic Bartter syndrome).
- Familial hypomagnesemia with hypercalciuria and nephrocalcinosis (FHHNC):
  - FHHNC is an autosomal recessive condition caused by mutations in either the *CLDN-16* or *CLDN-19* genes.
  - FHHNC often presents in childhood with seizures or tetany caused by hypomagnesemia.
  - Other clinical manifestations include frequent urinary tract infections (UTI), polyuria, polydipsia, failure to thrive, nephrolithiasis, and progressive renal failure.
  - Homozygous *CLDN*-16 or -19 mutations are associated with impaired tight junction integrity in the thick ascending limb of the loop of Henle, urinary magnesium and calcium wasting, and hypomagnesemia.
  - Patients usually develop the characteristic triad of hypomagnesemia, hypercalciuria, and nephrocalcinosis.
  - Profound visual impairment characterized by macular coloboma, significant myopia, and horizontal nystagmus can been seen in association with *CLDN-19* mutations.
- Distal renal tubular acidosis (dRTA):
  - Primary dRTA is an inherited condition characterized by systemic acidosis as a result of the inability of the distal tubule to adequately acidify the urine.
  - Failure to thrive, polyuria, polydipsia, hypercalciuria, hypocitraturia, nephrocalcinosis, renal calculi, and hypokalemia are common presenting signs in infancy.

  - Primary dRTA may be a dominant (*SLC4A1* gene) or a recessive condition (*ATP6V1B1* or *ATP6V0A4* genes).
  - The inability to secrete H^+ ions from the α-intercalated cells of the distal tubule is caused by either a defective vacuolar H^+-ATPase (*ATP6V1B1* or *ATP6V0A4* genes) or a defective $Cl^-/HCO3^-$ anion exchanger-1 (*SLC4A1* gene).
  - Sensorineural hearing loss may be found in patients with *ATP6V1B1* mutations.
- Hereditary hypophosphatemic rickets with hypercalciuria (HHRH):
  - HHRH is a rare, autosomal recessive disorder caused by mutations in the *SLC34A3* gene, resulting in loss-of-function of the type IIc sodium phosphate cotransporters of the proximal tubule.
  - The decreased renal phosphate reabsorption can result in profound hypophosphatemia, normocalcemia, rickets, and bone pain.
  - Hypercalciuria and nephrolithiasis are also commonly observed and may be the result of a hypophosphatemia-induced stimulation of 1, 25-dihydroxyvitamin D synthesis.
  - The increased synthesis causes increased gastrointestinal absorption of calcium and excessive urinary calcium losses in the face of normal serum calcium levels.
- Hyperoxaluria:
  - Oxalate is an end product of the metabolic pathways for glyoxylate and ascorbic acid and is primarily excreted by the kidneys.
    - The vast majority (80–85 %) of daily urinary oxalate excretion is derived from normal metabolic homeostasis.
    - The remainder (10–15 %) is from dietary intake.
  - Daily urine oxalate excretion is generally less than 50 mg/day/1.73 m^2 of body surface area.
  - The random urine oxalate to creatinine ratio can be used to estimate oxalate excretion.
  - Increased urinary oxalate excretion may be caused:
    - By an inherited metabolic disorder (primary hyperoxaluria [PH]).
    - Or, more commonly, as a secondary phenomenon caused by increased oxalate absorption or excessive intake of oxalate precursors.
  - Primary hyperoxaluria (PH):
    - PH type I and II are relatively rare, autosomal recessive disorders of endogenous oxalate production.
    - Overproduction of oxalate by the liver causes excessive urinary oxalate excretion with resultant nephrocalcinosis and nephrolithiasis.
    - The calcium oxalate deposition results in progressive renal damage; however, the clinical presentation can vary from end-stage renal failure in the neonate to occasional stone passage into adulthood.
    - Because of the clinical variability, the diagnosis is often overlooked and only realized after the loss of a transplanted kidney.
    - PH type I is caused by mutations in the *AGXT* gene, which result in a functional defect of the hepatic peroxisomal enzyme alanine–glyoxylate aminotransferase (AGT).
    - The deficit leads to accumulation of glyoxylate, glycolate, and oxalate in the urine.
    - Pyridoxine is an essential cofactor for proper AGT activity and, rarely, profound vitamin B6 deficiency can mimic PH type I.
    - PH type II is caused by mutations in the *GRHPR* gene with resultant deficient glyoxylate reductase–hydroxypyruvate reductase enzyme activity.
    - Excessive amounts of oxalate and l-glyceric acid are excreted by the kidney.
    - PH type II is somewhat milder compared with PH type I but is not benign.
    - Recently, a third variant, PH type III has been described in eight families with hyperoxaluria and mutations in the *DHDPSL* gene.
    - The exact mechanism by which hyperoxaluria occurs in PH type III is yet to be fully elucidated.

  - Secondary hyperoxaluria:
    - Secondary hyperoxaluria is caused by:
      - A dietary exposure to large amounts of oxalate (or oxalate precursors).
      - An underlying disorder that causes increased absorption of dietary oxalic acid from the intestinal tract.
    - Gastrointestinal absorption varies inversely with dietary calcium intake, and, as a result, calcium-deficient diets may increase oxalate absorption and hyperoxaluria.
    - Oxalate is a byproduct of ascorbic acid metabolism, and high doses of vitamin C have also been associated with hyperoxaluria.
    - Increased dietary absorption is usually characterized by fat malabsorption or chronic diarrhea.
    - Other causes of secondary hyperoxaluria include:
      - Inflammatory bowel disease
      - Celiac disease
      - Exocrine pancreatic insufficiency (cystic fibrosis)
      - Biliary tract disease
      - Small bowel resection or short bowel syndrome
    - The pathogenesis in these conditions results from the presence of free fatty acids that bind calcium in the intestinal lumen resulting in more unbound oxalate, which is free to be absorbed.
- Hypocitraturia:
  - Citrate is normally present in the urine and regulated through a process of both absorption and metabolism at the level of the proximal tubule.
  - Hypocitraturia is generally defined as a citrate to creatinine ratio of less than 180 mg/gm in men and less than 300 mg/gm in women on a 24-h urine collection.
  - Intracellular acidosis of the proximal tubule, caused by either metabolic acidosis or hypokalemia results in an increased citrate absorption in the proximal tubule and resultant hypocitraturia.
  - Hypocitraturia results from:
    - Ketogenic diet
    - Certain medications (topiramate, zonisamide, and acetazolamide)
    - Distal renal tubular acidosis (dRTA)
    - Chronic diarrhea
  - Given that an incomplete dRTA can occur in the absence of an overt systemic acidosis or hypokalemia, the condition can often be overlooked in the face of hypocitraturia if provocative acid-load testing is not readily available.
  - Despite these known associations, most cases of hypocitraturia are idiopathic although a diet rich in animal protein and low in vegetable fiber and potassium seems to promote lower citrate excretion.
- Cystinuria:
  - Cystinuria is an autosomal recessive disorder caused by mutations in either the *SLC3A1* or the *SLC7A9* genes.
  - The end result is a disordered amino acid transport in the proximal tubule.
  - Cystinuria is characterized by urinary hyperexcretion of cystine and the dibasic amino acids lysine, ornithine, and arginine.
  - Normal individuals excrete less than 50–60 mg of cystine/day/1.73 m^2 of body surface area, whereas patients who are homozygous for cystinuria often excrete greater than 400 mg/day/1.73 m^2 of body surface area.
  - Patients typically present with renal colic and urolithiasis in the second or third decade of life; however, they may present as early as infancy with staghorn calculi.
  - The poor solubility of cystine in the urine causes precipitation in the collecting system, which, if left untreated, usually results in recurrent episodes of calculi and long-term risk for renal failure.
  - Associated urinary tract infections are common, and combined cystine and struvite calculi have been reported.
  - In cystinuria, the disordered cystine transport primarily results from dysfunction of the heteromeric amino acid transporter (rBAT/$b^{0,+}$AT), comprising heavy (rBAT) and light ($b^{0,+}$AT) subunits.
  - Cystinuria was originally classified into type I and non–type I (types II and III) based on the urinary cystine concentration pattern of obligate heterozygotes and the presumed mode of inheritance.

  - Type I follows the classic autosomal recessive inheritance with heterozygotes showing normal cystine excretion.
  - In contrast, non–type I (type II and III) heterozygotes demonstrate moderate or high excretion of urinary cystine.
  - Types II and III differ in that type III homozygotes show a nearly normal increase in cystine plasma levels after oral cystine administration.
  - It is now clear that homozygous mutations in the *SLC3A1* gene, which encodes rBAT is associated with type I cystinuira, and homozygous mutations in the *SLC7A9* gene, which encodes $b^{0,+}$AT accounts for most cases of type II and III.
  - A more recent classification system has been developed:
    - Cystinuria type A: Patients who are homozygous for the *SLC3A1* mutations.
    - Cystinuria type B: Patients who are homozygous for the *SLC7A9* mutations
    - Cystinuria type C: Patients who have a mutation in both the *SLC3A1* and *SLC7A9* genes.
- Hyperuricosuria:
  - Uric acid excretion is greater in children than in adults, with the highest urinary fractional excretion (Fe) found in neonates (Fe 30–50 %) and levels reaching adult values (Fe 8–12 %) in adolescence.
  - Hyperuricosuria is defined as uric acid excretion of greater than 815 mg/day/1.73 m^2 of body surface area.
  - When adjusted for glomerular filtration rate (GFR), relative uric acid excretion is fairly constant after 2 years of age.
  - In children who are not yet trained to use toilet but older than of 2 years, hyperuricosuria can be defined as greater than 0.56 mg/dL of GFR on a spot urine collection.
  - This value may be calculated using Equation:

$$\bullet \quad \text{Urine uric acid } (\text{mg}/\text{dL}) \times \text{Plasma creatinine } (\text{mg}/\text{dL}) / \text{Urine creatinine} (\text{mg}/\text{dL}).$$

  - Hyperuricosuria in the setting of low urinary pH is the greatest risk factor for uric acid stone formation.
  - Hyperuricosuria associated with significant hyperuricemia is usually associated with:
    - Inherited disorders of purine metabolism
    - Lymphoproliferative disorders
    - Polycythemia
  - Rarely, a condition known as hereditary renal hypouricemia characterized by low serum uric acid, hyperuricosuria, nephrolithiasis, and exercise-induced acute renal failure has been reported.
  - Mutations in either the *SLC22A12* or the *SLC2A9* genes, both of which encode urate transporters expressed in the proximal tubule, are known to be causative factors of hyperuricosuria.
  - Other causes of hyperuricosuria include:
    - Excessive purine intake (animal protein, anchovies, and mussels)
    - Hemolysis
    - Uricosuric medications (probenecid, salicylates, and losartan)
    - Cyanotic congenital heart disease
    - Melamine toxicity
    - Idiopathic (familial) hyperuricosuria
  - There is also a phenomenon primarily observed in adults called hyperuricosuric calcium oxalate urolithiasis in which hyperuricosuria seems to be the principle contributor to the development of calcium oxalate stones with either no or minimal uric acid content (epitaxy).
- Inherited disorders of purine metabolism:
  - Phosphoribosyl pyrophosphate synthetase superactivity (PRPSS):
    - This is an X-linked condition caused by mutations in the *PRPS1* gene.
    - The overactive PRPSS is associated with excessive purine production.
    - The subsequent purine degradation results in hyperuricemia, gout, hyperuricosuria, and uric acid nephrolithiasis.

    - Some affected individuals have neurodevelopmental abnormalities, particularly sensorineural deafness.
  - Hypoxanthine-guanine phosphoribosyl transferase (HPRT) deficiency:
    - This is an X-linked inborn error of purine metabolism caused by mutations in the *HPRT1* gene associated with overproduction of uric acid.
    - Complete deficiency of HPRT activity is associated with the Lesch-Nyhan syndrome, characterized by mental retardation, spastic cerebral palsy, choreoathetosis, uric acid calculi, and self-injurious behavior.
    - Children with partial HPRT deficiency can be phenotypically similar to patients with complete deficiencies or may have more subtle or mild neurologic symptoms.
    - Renal stones, uric acid nephropathy, renal obstruction, or gout may be the first presenting signs of the disease.

9.3 Classification of Urolithiasis

- Urolithiasis are considered relatively rare in children.
- In Europe, kidney stones occur in one to two children per million population per year.
- This however is not the case nowadays and a significant increase in the number of children diagnosed with and treated for urolithiasis has occurred in the last decade.
- Children with stones now account for 1 in 685 pediatric hospitalizations in the United States.
- Surprisingly, more than half the patients are younger than 13 years at hospitalization.
- In underdeveloped countries, children more frequently have endemic bladder stones than renal stones.
- Endemic bladder calculi are common in developing countries where dietary protein is mostly derived from plant sources rather than meat. These areas include:
  - Eastern Europe
  - Southeast Asia
  - India
  - The Middle East
- Upper urinary calculi associated with urease-producing bacterial infection occur in England and Europe.
- In children, calcium stones are most common.
- In children urolithiasis occur with almost equal frequency among boys and girls. The boy-to-girl ratio is 3:2.
- Urinary stones are typically classified by their location or by their chemical composition.
- Urinary stones are classified according to their location as follows:
  - Renal
  - Ureteric
  - Vesical
  - Urethral
- Urinary stones are classified according to their chemical composition as follows:
  - Calcium-containing
  - Struvite
  - Uric acid
  - Other compounds
- Calcium oxalate is a major constituent of most urinary stones.
- Knowledge of composition of urinary stones is important as this may help to design preventive therapy.
- The approximate frequency of kidney stone types in the pediatric age group is:
  - Calcium with phosphate or oxalate (57 %)
  - Struvite (24 %)
  - Uric acid (8 %)
  - Cystine (6 %)
  - Endemic (2 %)
  - Mixed (2 %)
  - Other types (1 %).
- With children, particularly younger children, the primary cause of stone formation (e.g., hypercalciuria, hyperuricosuria) can usually be identified with a thorough evaluation.

9.4 Clinical Features

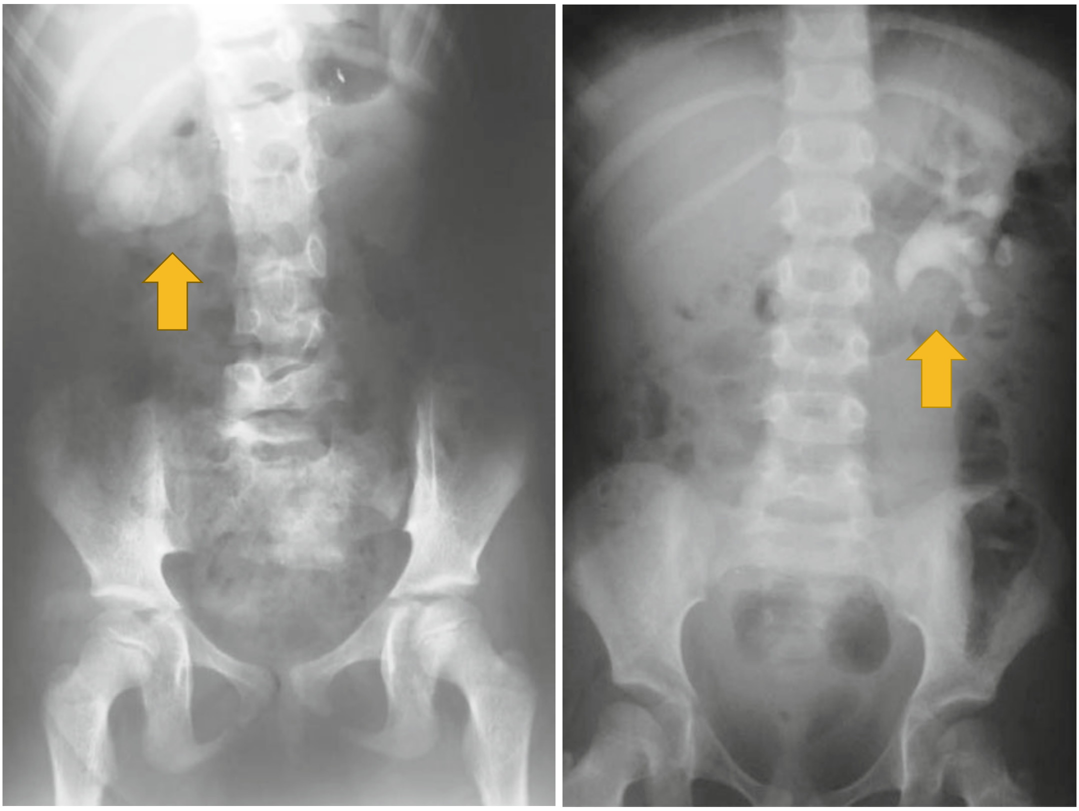
- The clinical manifestations of urolithiasis depends on the following factors:
  - The size of the stone
  - The location of the stone
  - The production of urinary outflow obstruction

  - The movement of the stone
  - The presence of infection
- Larger stones tend to be more symptomatic, although some large stones produce few symptoms.
- Sometimes small stones produce severe symptoms as a result of their movement.
- History should include questions to identify:
  - Frequent urinary tract infections
  - Frequent bouts of abdominal pain
  - Hematuria (gross or microscopic)
  - Passage of previous calculus
  - Dietary intake (e.g., oxalate, purine, calcium, phosphate, fructose, animal protein)
  - Drug intake (e.g., anticancer drugs, glucocorticoids, allopurinol, loop diuretics)
  - Vitamin intake (A, D)
  - Fluid intake, habitual fluid type (e.g., water, milk, tea, sports drinks),
- History should include questions to identify chronic disease:
  - Renal tubular acidosis
  - Inflammatory bowel disease
  - Short-gut syndrome
  - Intractable seizures
  - Cystic fibrosis
  - Prior urologic surgery (e.g., kidney transplant)
  - Recent immobilization
- A careful family history to identify other family members with stones is important.
  - In some reports, as many as 70 % of children with idiopathic hypercalciuria have a family history of stones. The cause of idiopathic hypercalciuria is unknown, but it may be transmitted as an autosomal dominant trait.
- Other inherited conditions to be considered during evaluation include:
  - Cystinuria, an autosomal recessive defect of amino acid transport that leads to cystine kidney stones.
  - Glycinuria, a rare inherited renal tubular defect producing oxalate stones.
  - Xanthinuria, an autosomal recessive disorder that produces xanthine urolithiasis.
  - Primary hyperoxaluria, produced by an autosomal disorder leading to oxalate stones.
  - Several inherited disorders in purine metabolism lead to uric acid stones (Lesch-Nyhan disease is probably the best known).
- The clinical presentation of urolithiasis are variable and include:
  - Symptoms differ according to the location of the stone.
  - Intense pain that suddenly occurs in the back and radiates downward and centrally toward the lower abdomen or groin.
  - The pain may be dull aching localized to the renal area or lower abdomen in those with urinary bladder stones.
  - The pain may be nonspecific localized to the abdomen, flank, or pelvis.
  - Sometimes the pain is severe colicky localized to the flanks, abdomen or pelvis or radiates from the flank downwards towards the urinary bladder and urethra.
  - In infants and children and because of rarity of urolithiasis, the pain may be attributed to intestinal colic.
  - Hematuria, usually gross, occurring with or without pain.
  - Hematuria may or may not be present or may be microscopic.
  - Macroscopic or microscopic hematuria can occur in up to 90 % of children with urolithiasis.
  - Urinary tract infection may be the first presentation of urolithiasis.
  - Unexplained sterile pyuria or recurrent urinary tract infections (UTIs) should raise the level of suspicion for urolithiasis, especially in the younger child.
  - Urolithiasis may be discovered incidentally during radiological investigation of children with urinary tract infection.
  - Asymptomatic urolithiasis may be discovered during radiological investigation for another reason.
  - Persistent microscopic hematuria, which consists of five or more RBCs per high-power field in three of three consecutive centrifuged urine specimens obtained at least 1 week apart may be the presentation of urolithiasis in children.
  - Ureteral stones are much more likely to cause obstruction that leads to severe

  colicky or non-specific flank or abdominal pain.
  - Renal stones may be found incidentally and remain present for years without causing symptoms.
  - Approximately 10 % of calculi can present with fever, dysuria and urinary frequency and are usually localized to the lower urinary tract.
  - Urolithiasis may also be complicated by urinary tract infection. These patients may be asymptomatic or present with dysuria and frequency. Pyuria may also be present without bacteriuria or infection.
  - Rarely, a urethral stone can present with acute urinary obstruction and urine retention.
- Nephrocalcinosis:
  - Nephrocalcinosis is mostly asymptomatic, especially during infancy and early childhood.
  - Sometimes, nephrocalcinosis is discovered incidentally on an imaging study performed for other reasons.
  - Nephrocalcinosis may also be discovered when symptoms of reduced concentrating capacity of the renal tubules are obvious.
  - It is not unusual for nephrocalcinosis to be diagnosed during systematic renal ultrasound examination of high-risk infants or as part of the diagnostic evaluation of urinary tract infection.
  - The first clinical symptoms, if any of nephrocalcinosis, are gross or microscopic hematuria and/or sterile leukocyturia that may be misdiagnosed as urinary tract infection.

9.5 Investigations

- Complete blood count (CBC)
- Electrolyte, blood urea nitrogen (BUN), creatinine
- Serum calcium, phosphorus, alkaline phosphatase, uric acid, total protein, albumin, parathyroid hormone (PTH), and vitamin D metabolite levels
- Urinalysis and culture
- Estimating the ratio of calcium, uric acid, oxalate, cystine, citrate, and magnesium to creatinine.
- A 24-h urine collection for calcium, phosphorus, magnesium, oxalate, uric acid citrate, cystine, protein, and creatinine clearance.
- Renal ultrasonography is very effective for identifying stones in the urinary tract.
- Generally, ultrasonography should be used as a first study.
  - US remains the initial study of choice in the assessment of calculi in children.
  - Ultrasound has the ability to detect 90 % of calculi confined to the kidney.
  - The sensitivity for detecting ureteral calculi and smaller calculi (<5 mm) is poor.
- If no stone is found but symptoms persist, abdominal CT-scan is indicated.
- Abdominal CT-scan is the most sensitive test for identifying stones in the urinary system. It is safe, rapid, and has been shown to have 97 % sensitivity and 96 % specificity.
- Many radiopaque stones can be identified with a simple abdominal radiogram (Figs. 9.1 and 9.2).
- Calculi composed of uric acid, cystine, xanthine, or indinavir are usually radiolucent.
- The typical stone location is within the renal pelvis and/or the renal calyces or the ureter and less often within the bladder.
- The most common ureteral calcification is a stone that has migrated down from the kidney. These stones typically become impacted at anatomic sites of narrowing and are especially difficult to detect when they overlie bony structures such as the sacrum.
- Detection of a ureteral stone via ultrasonography is difficult, but the stone may lead to obstruction (hydroureter or hydronephrosis) and may, thus, be suspected, even if not directly visualized.
- Non-contrast-enhanced CT is more effective than intravenous urography (IVU) in identifying and locating ureteral stones.
- Intravenous pyelography is rarely used in children (Fig. 9.3).
- An intravenous urography can be considered in children with hypercalciuria in whom medullary sponge kidney is suspected.



Figs. 9.1 and 9.2 Abdominal x-rays showing radio-opaque stones in two children. Note the staghorn stone in the second x-ray

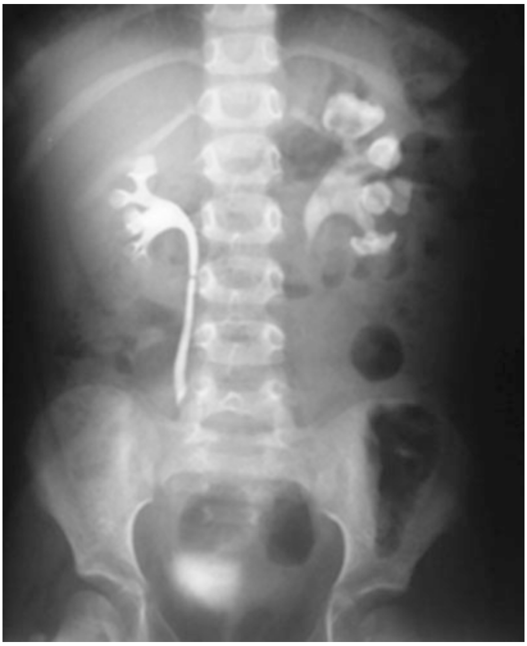


Fig. 9.3 An intravenous urography showing a large left staghorn calculus

- The content of the stone (i.e., cysteine versus calcium versus uric acid) may be the most important element in developing a treatment program to prevent further stone formation.
- Specific Metabolic Investigations:
  - Urolithiasis developing during childhood carry a life-long risk of stone formation.
  - Approximately 16–20 % of children develop recurrences within 3–13 years of the first attack.
  - Children with an identifiable metabolic abnormality have an up to fivefold increased risk of having a recurrence as compared with children with no identifiable metabolic disorder.
  - All children should undergo a comprehensive initial evaluation.
  - An infrared spectroscopy or radiograph diffraction analysis of a passed stone is important.
  - If a cystine or struvite stone is found, the analysis will be diagnostic.

  - Serum and urine studies should be obtained in patients in whom stone analysis could not be performed or for those with either calcium or uric acid-based stones.
  - A serum creatinine level is essential to evaluate for possible acute kidney injury or chronic kidney disease.
  - Serum calcium, phosphorous, bicarbonate, magnesium, and uric acid levels are effective in screening for hypercalcemia- and hypocalcemia-associated calculi, hyperuricemia, HHRH, Bartter syndrome, dRTA, and FHHNC.
  - Primary hyperparathyroidism is rare in children and measurement of parathyroid hormone level is indicated if there is evidence of hypercalcemia and hypophosphatemia.
  - A 25-hydroxyvitamin D level should be evaluated in all patients with hypercalcemia.
  - A spot urine beta-2 microglobulin (low-molecular-weight protein) is a useful screening test for Dent disease.
  - A 24-h urine collection should be analyzed for calcium, oxalate, uric acid, sodium, citrate, creatinine levels, volume, pH, and cystine.
  - Measuring the ratio of calcium, uric acid, citrate, and oxalate levels to creatinine level in a random urine sample.

9.6 Complications of Urolithiasis

- The primary complications of urolithiasis include:
  - Obstruction of the urinary tract
  - Renal parenchymal damage
  - Recurrent urinary tract infection

9.7 Management

- The management of children with urolithiasis include:
  - To diagnose children with asymptomatic urolithiasis and treat those with symptomatic urolithiasis.
  - To prevent renal damage, which may lead to loss of renal parenchyma.
  - To expedite passage or removal of any stones present.
  - To treat associated urinary tract infection.
  - To diagnose those with predisposing conditions for urolithiasis.
  - To prevent new stones from forming.
- A child presenting with acute renal colic can be managed with analgesics.
- This can be accomplished using simple non-steroidal analgesics.
- Narcotics may be required in those with severe pain, as well as enteral or parenteral hydration.
- In the absence of oligoanuric renal failure or a complete urinary obstruction, an intravenous infusion rate of 1.5–2 times their maintenance is recommended.
- A small stone stuck at the ureteropelvic or ureterovesical junction may pass spontaneously and these patients should be treated initially conservatively.
- A stone that completely obstructs the bladder outlet should be treated with catheterization using a Foley's catheter to relive the obstruction.
  - The obstructing stone can then be removed from the urinary bladder.
  - There are several methods to remove the stone:
    - Vesicostomy and stone removal
    - Cystoscopy, stone crushing and removal
    - Lithotripsy
- Children with asymptomatic stones detected while screening for another problem should have blood and urine testing performed to identify underlying metabolic abnormalities.
- The specific aims of surgical treatment of urolithiasis include:
  - Drainage and removal of the obstruction of the urinary tract
  - Removal of stones present in the urinary tract
  - Surgical correction of anatomic abnormalities, which may promote additional stone formation.
- A child with an infected stone and urinary tract infection should be treated with antibiotics and drainage of the urinary tract in the presence of obstruction.

- Stones removal technique used usually depends on the stone size and location and these include:
  - Ureteroscopic stone extraction
  - Percutaneous nephrolithotomy
  - Open stone extraction
  - Extracorporeal shockwave lithotripsy (ESWL).
- Alpha-1 adrenergic blocker agents, such as doxazosin, have been used as medical expulsive treatment in children with distal uretral stones.
- Dietary considerations depend on the type of stone.
- A high fluid intake leading to increased urine output is safe and generally beneficial for children with all types of stones.
- A dietitian is important in those with dietary induced urolithiasis. Children with stones composed of calcium and who have excessive calcium intake or idiopathic gastrointestinal absorptive hypercalciuria may benefit from lowered dietary calcium intake.
- The goal is to lower urinary calcium such that no new stones are formed without producing calcium deficiency.
- Fluids that increase urinary pH and citrate excretion such as orange juice, lemonade, and black currant juice, as well as those that increase urinary volume such as coffee, tea, beer, and wine, reduce the risk of calcium stone formation.
- Grapefruit juices seem to increase the risk of calcium-based stones.
- Increased sodium intake is known to promote calciuria by competing for reabsorption at the level of the renal tubules.
- A low salt diet corresponding to less than 2–3 mEq/kg/day in children or less than 2.4 g/day in adolescents or adults is generally recommended for patients with hypercalciuria or calcium-containing stones.
- A low salt diet may also reduce urinary cystine excretion in patients with cystinuria.
- A higher calcium containing diet is associated with a reduced risk of stone formation.
- Higher calcium intake effectively binds dietary oxalate in the gut, thereby reducing intestinal absorption and eventual urinary oxalate excretion.
- Calcium restriction is not recommended, in part, because of the long-term risk of osteoporosis.
- Excess consumption of vitamin D with or without calcium supplements can also induce excessive urinary calcium excretion.
- Excessive dietary animal protein intake causes increased urinary calcium excretion and reduced urinary pH and citrate excretion.
- Children with idiopathic hypercalciuria caused by renal tubular calcium leak may benefit from treatment with a thiazide.
- In those with idiopathic gastrointestinal absorptive hypercalciuria and not responding to a low-calcium diet, neutral sodium phosphate may be beneficial in reducing dietary calcium absorption.
- Hypocitraturia is treated with oral potassium citrate. Supplemental citrate leads to correction of hypocitraturia.
- Struvite stones require treatment with an appropriate antibiotic.
  - Surgical intervention or ESWL may be necessary if the stone produces high-grade obstruction, if antibiotic therapy is not adequately eliminating infection, or after infection is cleared to remove stone fragments.
- Uric acid stones require alkalinization of urine with sodium bicarbonate or potassium citrate in four divided doses.
  - Urine pH levels should be maintained at 7.5 or greater.
  - Uric acid is much more soluble in alkaline than acid urine.
  - Allopurinol is indicated in children with uric acid stones whose daily uric acid excretion exceeds the reference range.
  - The consumption of excessive amounts of dietary animal protein also results in increased purine intake, increased uric acid production, and may contribute to both uricosuria and more acidic urine.
  - The treatment of children with uric acid calculi includes:
    - A high urine flow rate
    - Alkalization of the urine
    - Allopurinol (4–10 mg/kg/day, adult maximum 300 mg/day) is indicated in

    those with hyperuricemia and hyperuricosuria, such as PRPSS or HPRT deficiency.
    - Inhibition of xanthine dehydrogenase by allopurinol may lead to the accumulation and urinary excretion of xanthine.
    - Rarely, a secondary xanthinuria with xanthine calculi is observed in children on long-term therapy.
    - Allopurinol may also be the agent of choice for treating hyperuricosuric calcium oxalate urolithiasis if there is no concomitant evidence of hypercalciuria, hyperoxaluria, or hypocitraturia.
- The medical management of cystinuria consists of:
  - Hyperhydration
  - Urine alkalization
  - Sulfhydryl agents such as tiopronin
  - Reducing animal protein intake might be helpful by increasing urinary pH
- Patients with calcium oxalate stones who demonstrate evidence of hyperoxaluria should have limited dietary oxalate ingestion.
  - Foods that contain high levels of oxalate include certain nuts (almonds, peanuts, cashews, walnuts, and pecans), spinach, soy beans, tofu, rhubarb, beets, sweet potatoes, wheat bran, okra, parsley, chives, black raspberries, star fruit, green tea, and chocolate.
- Vitamin C supplements have been associated with increased risk of calcium oxalate stone formation because oxalate is a byproduct of ascorbic acid metabolism.
- Vitamin C supplements should be discontinued in calcium oxalate stone formers with hyperoxaluria.
- Potassium-rich foods such as fruits and vegetables usually contain large amounts of citrate, which are protective against the formation of calcium oxalate stones.
- A diet high in potassium is protective against urolithiasis.
- A potassium-restricted diet can cause increased urinary calcium excretion and overt hypokalemia, leading to hypocitraturia.
- Higher dietary magnesium has been associated with a lower risk of stone formation, and magnesium supplement may be helpful in the treatment of children with secondary hyperoxaluria.
- Carbohydrate ingestion has been associated with hypercalciuria, and sucrose ingestion has been found to be associated with urolithiasis.
- Phyate, a dietary factor found in many high fiber-containing foods (cereals, legumes, vegetables, and nuts), seems to bind calcium avidly and may inhibit the formation of calcium oxalate stones.
- Medications:
  - A thiazide diuretic is often required for children with hypercalciuria who do not respond to a restricted sodium diet.
  - The usual recommendation is hydrochlorothiazide 1–2 mg/kg/day (adult 25–100 mg/day).
  - Amiloride can be added for its potassium-sparing effect as well as for its ability to independently reduce calcium excretion.
  - Thiazide diuretics have also been used in an attempt to reduce calcium excretion in patients with Dent disease, FHHNC, and PH.
  - Treatment with either potassium citrate (2–4 mEq/kg/day) or potassium-magnesium citrate has been shown to reduce the recurrence of calcium oxalate stone formation in patients with low or normal citrate excretion.
  - Sodium citrate is generally considered less ideal because it is associated with increased sodium delivery to the nephron.
  - Potassium citrate is also used to alkalinize the urine in patients with Dent disease, FHHNC, dRTA, uric acid urolithiasis (goal of urine pH >6.5), cystinuria (goal of urine pH >7), and hyperoxaluria.
  - Thiol-containing agents (d-penicillamine and α-mercaptopropionylglycine) are used exclusively for patients with cystinuria in whom fluid and dietary modifications as well as urinary alkalization are ineffective in preventing stone recurrences or dissolving preexisting stones.

- The thiol group combines with cysteine to form a more soluble cysteine-drug product combination, which is be excreted.
- Approximately 10–30 % of children with primary hyperoxaluria type I are pyridoxine sensitive. The treatment should be initiated (2–5 mg/kg/day) and increased gradually (8–10 mg/kg/day). Large doses of pyridoxine have been known to induce sensory neuropathies.

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Persistent Müllerian Duct Syndrome (PMDS)

10

10.1 Introduction

- Persistent Müllerian duct syndrome (PMDS) is a rare disorder of sexual development.
- It was first described by Nilson in 1939.
- It is also called persistent oviduct syndrome.
- It is considered by some to be a form of pseudohermaphroditism due to the presence of Müllerian derivatives.
- This syndrome is characterized by the persistence of Mullerian duct derivatives (i.e. uterus, cervix, fallopian tubes and upper two thirds of vagina) in a phenotypically (normal male reproductive organs and normal male external genitalia) and karyotypically (46, XY) male patient.
- Persistent Müllerian duct syndrome is usually caused by deficiency of fetal anti-Müllerian hormone (AMH) effect due to mutations of the gene for AMH or the anti-Müllerian hormone receptor, but may also be as a result of insensitivity to AMH of the target organ.
- PMDS is caused by mutations in the *AMH* gene (PMDS type 1) or *AMHR2* gene (PMDS type 2) and is inherited in an autosomal recessive manner.
- It affects males who have normal chromosomes (46, XY) and have normal male reproductive organs and normal male external genitalia.
- Persistent Müllerian duct syndrome affects only males and is inherited in an autosomal recessive pattern.
- Affected males with this disorder have normal male reproductive organs. They also have internal female reproductive organs (a uterus and fallopian tubes).
- The clinical features of PMDS depends on the mobility of the Müllerian derivatives (the uterus and fallopian tubes) which leads to either cryptorchidism or inguinal hernia. If the uterus and fallopian tube are mobile, they may descend into the inguinal canal during testicular descent. However, if the Müllerian derivatives are relatively immobile testicular descent may be impeded and the patient presents with undescended testes either unilateral or bilateral.

10.2 Embryology of Persistent Müllerian Duct Syndrome

- The normal sexual differentiation depends on the genetic sex (XX or XY), which is established at the time of conception.
- Following conception, the fetus is sexually indifferent with two different bipotential gonads and two pairs of internally developing Wolffian and Müllerian ducts.
- These two undifferentiated bipotential gonads develop from the urogenital ridge and ultimately develop into either a testis or an ovary.
- In addition to these bipotential gonads, fetuses of both sexes have also two sets of internal ducts: the Müllerian ducts and the Wolffian

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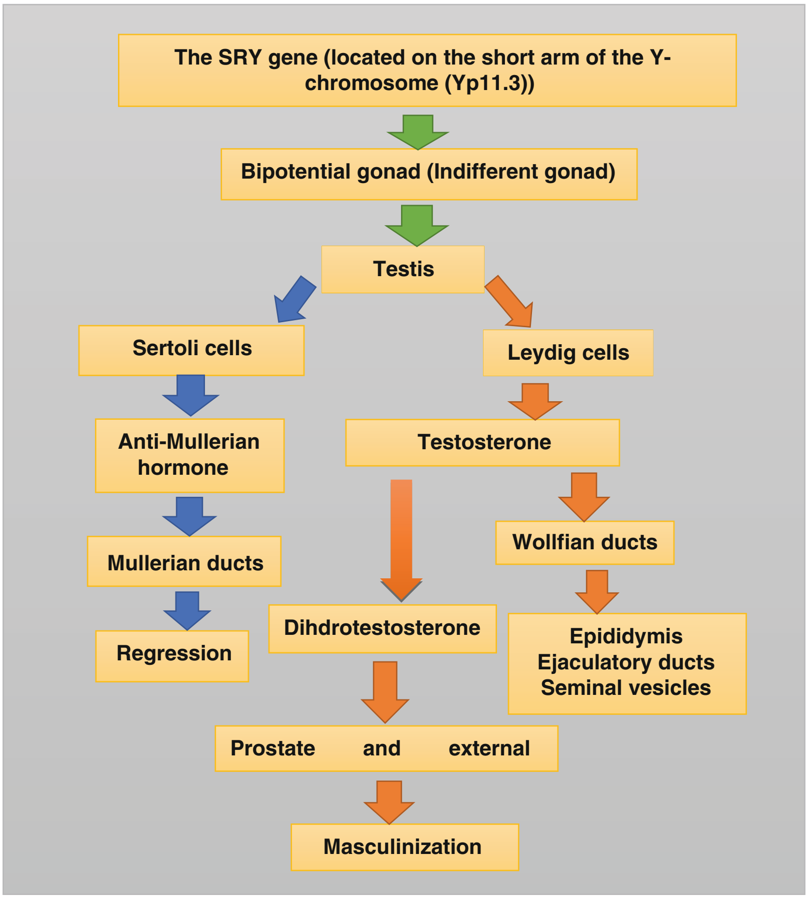
A.H. Al-Salem, *An Illustrated Guide to Pediatric Urology*, DOI 10.1007/978-3-319-44182-5_10

ducts which develop by 6–7 weeks of intrauterine life.

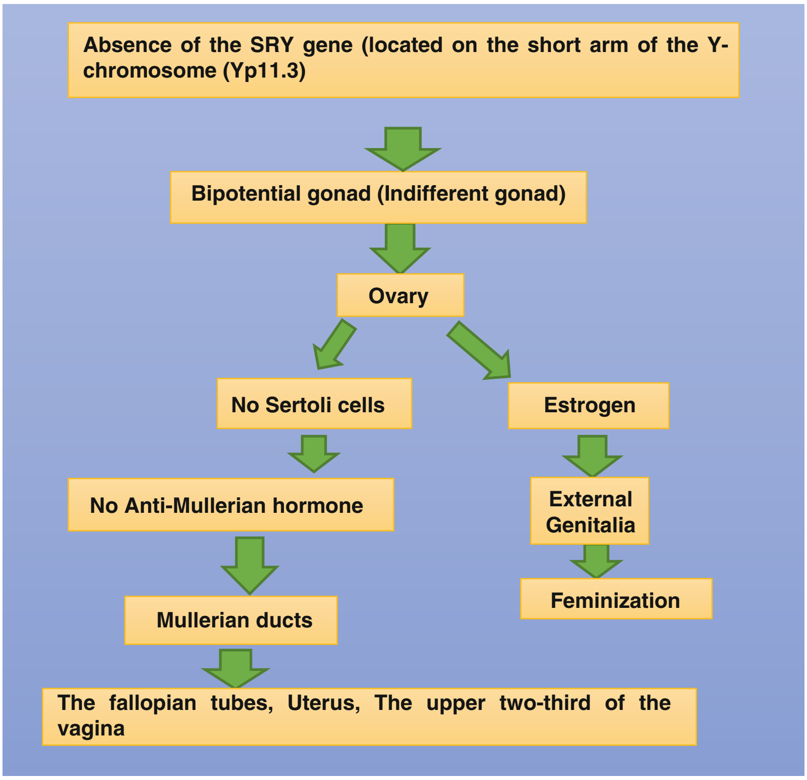
- Expression of sex-determining genes on the early bipotential gonad promotes development of the gonad into either a testis or an ovary.
- Various genes expressed by the Y chromosome at very specific times during development are responsible for the differentiation of the testes.
- In a male fetus, the testis differentiates by the end of the seventh gestational week.
- A 35-kilobase (kb) gene determinant located on the distal short arm of the Y chromosome, known as the *SRY* (sex determining region of the Y chromosome) is responsible for initiating the indifferent gonads to develop into testes.
- *SRY* codes for a transcription factor that acts in the somatic cells of the genital ridge.
- Expression of this gene triggers a cascade of events that ultimately leads to the development of testicular Sertoli and Leydig cells.
- *SRY* expression directs testicular morphogenesis, leading also to the production of MIS (Müllerian-inhibiting substance), and, later, testosterone.
- Normal sex differentiation is controlled by:
  - Testosterone
  - Dihydrotestosterone
  - Müllerian Inhibiting Factor (MIF).
  - Sertoli cells secrete MIF, which leads to regression of the Müllerian ducts.
  - Leydig cells secret testosterone which has a direct effect on the Wolffian ducts, and promotes their differentiation into the epididymis, vas deferens, and seminal vesicles.
  - Testosterone and under the influence of 5-alpha reductase is converted to Dihydrotestosterone which induces male differentiation of external genitalia.
  - Patients with PMDS have both Wolffian and Müllerian duct structures due to a deficiency of MIF.
- The external genitalia at 6–7 weeks gestation appear female and include a genital tubercle, the genital folds, urethral folds and a urogenital opening. These subsequently differentiate into male or female external genitalia under the influence of estrogen or dihydrotestosterone.
- Male Differentiation:
  - The male sexual differentiation depends on two important steps:
    - The development of the bipotential gonad into a testis.
    - Internal and external genitalia differentiation.
  - The development of the bipotetial gonad into a testis occurs at about the sixth week of gestation under the influence of the SRY gene.
    - The SRY gene is located on the short arm of the Y-chromosome (Yp11.3). It is responsible for initiating sex differentiation by downstream regulation of sex-determining factors.
    - This involves expression of several genes including WT1, CBX2 (M33), SF1, GATA4/FOG2 is critical to SRY activation.
    - The SOX9 gene, located on 7q24.3-25.1, is essential for early testis development.
  - The second step in male sex differentiation involves internal and external genitalia differentiation.
  - The developed testes have two types of cells:
    - The Leydig cells
    - The Sertoli cells
  - The Sertoli cells produce the anti-Müllerian hormone (AMH).
  - The Leydig cells produce testosterone.
  - The AMH acts on its receptor in the Müllerian ducts and causes their regression.
  - Testosterone acts in a critical concentration-dependent and time-dependent manner to induce male sexual differentiation.
  - Testosterone acts on the androgen receptor in the Wolffian ducts to induce the formation of:
    - Epididymis

        - Ejaculatory ducts
        - Seminal vesicles.
    - The Leydig cells also produce insulin-like factor 3 (INSL3, relaxin-like factor), which play a role in the descent of testes to the scrotum.
    - Testesterone is also converted to dihydrotestosterone (DHT) under the influence of 5-alpha reductase enzyme, which acts on the androgen receptor of the prostate and external genitalia to cause its masculinization.
    - Binding of Testosterone and DHT to androgen receptors is necessary for androgen effect.

- Female Differentiation:
    - In females and as a result of the absence of SRY gene, the bipotential gonad develops into an ovary.
    - DAX1 gene is necessary for both testicular and ovarian development.
    - WNT4-signaling pathway plays a major role in ovarian development, Müllerian ducts development and ovarian steroidogenesis.
    - The second step in female sex differentiation involves internal and external genitalia differentiation.
    - Absence of the anti-Müllerian hormone (AMH) which is secreted by the testes leads to development of the Müllerian ducts.


The SRY gene (located on the short arm of the Y-chromosome (Yp11.3))
Bipotential gonad (Indifferent gonad)
Testis
Sertoli cells
Leydig cells
Anti-Mullerian hormone
Testosterone
Mulerian ducts
Wollfian ducts
Regression
Dihdrotestosterone
Epididymis
Ejaculatory ducts
Seminal vesicles
Prostate and external
Masculinization

- The Müllerian ducts give rise to:
  - The fallopian tubes
  - Uterus
  - The upper two-third of the vagina
- Absence of testesterone leads to regression of the Wollfian ducts.
- Estrogen secreted by the developing ovary leads to the development of the external genitalia of the female.
- In the female, the genital tubercle becomes the clitoris, the labio-scrotal folds become the labia majora, and the urethral folds become the labia minora.


Absence of the SRY gene (located on the short arm of the Y-chromosome (Yp11.3)
Bipotential gonad (Indifferent gonad)
Ovary
No Sertoli cells
Estrogen
No Anti-Mullerian hormone
External Genitalia
Feminization
Mullerian ducts
The fallopian tubes, Uterus, The upper two-third of the vagina

10.3 Etiology and Inheritance of PMDS

- This condition is usually caused by deficiency of fetal anti-Müllerian hormone (AMH) effect due to mutations of the gene for AMH or the anti-Müllerian hormone receptor, but may also be as a result of insensitivity to AMH of the target organ.
- AMH (Anti Müllerian Hormone) is produced by the primitive Sertoli cells as one of the earliest Sertoli cell products and induces regression of the Müllerian ducts.
- Fetal Müllerian ducts are only sensitive to AMH action around the seventh or eighth week of gestation, and Müllerian regression is completed by the end of the ninth week.
- The AMH induced regression of the Müllerian duct occurs in cranio-caudal direction via apoptosis.
- The AMH receptors are on the Müllerian duct mesenchyme and transfer the apoptotic signal to the Müllerian epithelial cell, presumably via paracrine actors.
- The Wolffian ducts differentiate into epididymis, vasa differentia and seminal vesicles under the influence of testosterone, produced by the fetal Leydig cells.
- Most people with persistent Müllerian duct syndrome have mutations in the *AMH* gene or the *AMHR2* gene.

- The *AMH* gene provides instructions for making a protein called anti-Müllerian hormone (AMH).
- The *AMHR2* gene provides instructions for making a protein called AMH receptor type II.
- The AMH protein and AMH receptor type II protein are involved in male sex differentiation.
- During development of a male fetus, these two proteins work together to induce breakdown (regression) of the Müllerian duct.
- Mutations in the *AMH* and *AMHR2* genes lead to nonfunctional proteins that cannot signal for regression of the Müllerian duct.
- As a result of these mutations, the Müllerian duct persists and goes on to form a uterus and fallopian tubes.
- Approximately 45 % of cases of persistent Müllerian duct syndrome are caused by mutations in the *AMH* gene and are called persistent Müllerian duct syndrome type 1.
- Approximately 40 % of cases are caused by mutations in the *AMHR2* gene and are called persistent Müllerian duct syndrome type 2.
- In the remaining 15 % of cases, no mutations in the *AMH* and *AMHR2* genes have been identified, and the genes involved in causing the condition are unknown.
- This condition is inherited in an autosomal recessive pattern. However, persistent Müllerian duct syndrome affects only males. Females with two mutated copies of the gene do not show signs and symptoms of the condition.
- PMDS type I results from mutations of the gene (*AMH*) for AMH on chromosome 19p3.3.
- PMDS type II results from mutations of the gene (*AMH-RII*) for the AMH receptor on 12q13.

10.4 Classification of PMDS

- Classically, patients with PMDS present with unilateral or bilateral cryptorchidism and they have normal male genotypes and phenotypes.
- Two anatomic variants of PMDS have been described: male and female.
  - The male form:
    - This is the most common form encountered in 80–90 % of cases.
    - It is characterized by unilateral cryptorchidism with contralateral inguinal hernia, and can be one of two types:
      - The first type is hernia uteri inguinalis, which is characterized by one descended testis and herniation of the ipsilateral corner of uterus and fallopian tube into the inguinal canal.
      - The second type is crossed testicular ectopia, which is characterized by herniation of both testes and the entire uterus with both fallopian tubes on the same side.
  - The female form:
    - This is seen in 10–20 % of cases.
    - It is characterized by bilateral cryptorchidism.
    - The gonads are usually within the pelvis, with the testes fixed within the round ligament in the ovarian position with respect to the uterus.

10.5 Clinical Features

- Patients with persistent Müllerian duct syndrome usually present with undescended testes (cryptorchidism) which can be unilateral or bilateral.
- More often, one testis has descended into the scrotum normally, and the other one has not. In these cases, the uterus and fallopian tubes are in the pelvis.
- In cases of unilateral or bilateral cryptorchidism associated with hernia, the possibility of PMDS should be kept in mind (Fig. 10.1).
- Sometimes they present with inguinal hernias (Fig. 10.2).
- Sometimes, the descended testis pulls the fallopian tube and uterus into the track through which it has descended and into the inguinal hernia sac. This condition is called hernia uteri inguinalis, a form of inguinal hernia in which the hernia sac contains the uterus and Fallopian tubes.
- In some cases with persistent Müllerian duct syndrome, they present with bilateral undescended testes and the undescended testis from one side is also pulled into the other side,

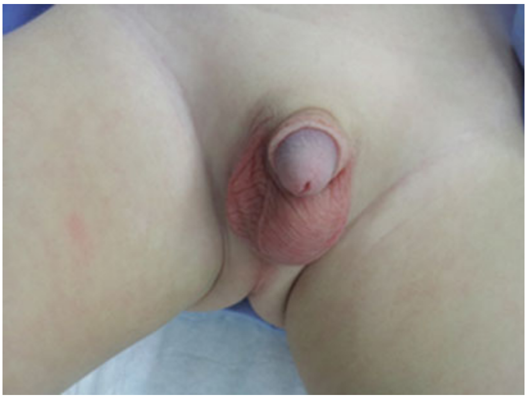


Fig. 10.1 A clinical photograph of a patient with normal looking external genitalia and undescended right testis who was found to have deficiency of MIS

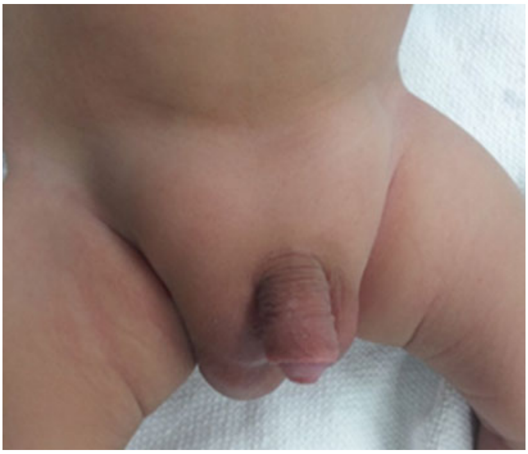


Fig. 10.2 A clinical photograph of a patient with normal looking external genitalia and a large right inguinal hernia who was found to have deficiency of MIS

forming an inguinal hernia with both undescended testes on the same side. This condition is called transverse testicular ectopia.

- The uterus and fallopian tubes are typically discovered intraoperatively when surgery is performed to treat undescended testes or inguinal hernia (Fig. 10.3).
- Sometimes the uterus and fallopian tubes are discovered preoperatively via ultrasound or MRI while investigating impalpable undescended testes or for other reasons.
- Some of these cases may remain undiagnosed to present late with infertility or blood in the semen (hematospermia). Infertility in these patients may be primary from the testes or secondary to obstruction or nonpatency of the vas deferens.
- Since the patients are phenotypically male, the diagnosis is usually not suspected and the diagnosis is delayed or made at the time of surgery for cryptorchidism or hernia.
- The risk of malignancy in an ectopic testis in a case of PMDS is similar to that in a cryptorchid testis in a healthy male. Germ cell tumors have been reported in the testis, whereas tumors of the Mullerian duct derivatives are very rare.

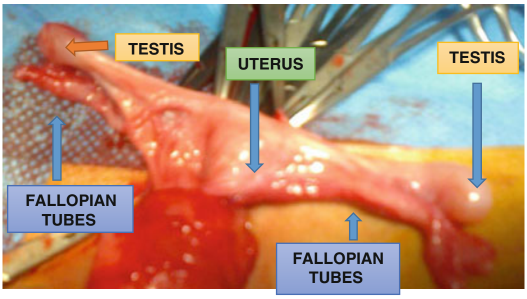


Fig. 10.3 A clinical intraoperative photograph of a patient with persistent Müllerian duct syndrome. Note the presence of a uterus, two fallopian tubes and two testes but no ovaries. This results from deficiency of MIS. Note also the testes fixed within the round ligament in the ovarian position with respect to the uterus

10.6 Treatment

- The aim of surgical treatment is to mobilize, preserve and fix the testes in the scrotum without injuring the vessels and vas.
- The associated hernia should also be treated.
- During surgery, the uterus is usually removed and attempts are made to dissect away Müllerian tissue from the vas deferens and epididymis without injuring them to improve the chance of fertility.
- A vas deferens is presents bilaterally, usually running close to the uterus.
- To avoid damage to the vas, care must be taken at the time of Müllerian remnants excision.
- Rarely, the vas deferens ends blindly.

- With the recent advances of minimal invasive surgery, laparoscopic hysterectomy is an alternative technique to improve the chances of fertility in these patients.
- The surgical management of PMDS includes:
  - Orchidopexy:
    - Every attempt should be made to preserve the testes, vas and vessels.
    - This may necessitates division of the uterus to lengthen the vas.
    - A transverse testicular ectopia may be associated with this condition. In this, both testes are found on the same side and both testes should be mobilized and fixed one in each scrotum.
  - Excision of Müllerian remnants:
    - This is not a simple procedure and care should be taken to avoid injury to the vas.
    - In those where removal of the Müllerian remnants is not possible, division of the uterus can be done to lengthen the vas and facilitates orchidopexy.
    - Removal of Müllerian remnants is unnecessary, since the remnants rarely produce symptoms and there is an extremely rare risk of subsequent malignancy.

10.7 Prognosis

- The prognosis depends upon the integrity of the testicular tissue and successful correction of cryptorchidism, which is often complicated by the close anatomical relationship between the vas deferens and the Mullerian derivatives
- The risk of malignancy in an ectopic testis in a case of PMDS is similar to that in a healthy male, with the incidence being 15 %. There have been case reports of embryonal carcinoma, seminoma, yolk sac tumor and teratoma in patients with PMDS, whereas tumors of the Mullerian duct derivatives are very rare.
- Infertility is common in these patients, with an absence of spermatozoa or results secondary to obstruction or nonpatency of the vas deferens.

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11

Neurogenic Bladder Sphincter Dysfunction

11.1 Introduction

- Neurogenic bladder sphincter dysfunction (NBSD) can develop as a result of a lesion at any level in the nervous system, including:
  - The cerebral cortex
  - The spinal cord
  - The peripheral nervous system
- In the pediatric age group, neurogenic bladder sphincter dysfunction can develop as a result of congenital or acquired causes.
- Commonly it results from congenital neural tube defects including:
  - Myelomeningocele
  - Lipomeningocele
  - Spina bifida
  - Sacral agenesis
  - Tethered cord
- Acquired causes include:
  - Spinal cord tumors
  - Spinal cord trauma
  - Transverse myelitis
- Neurogenic bladder is a term applied to a malfunctioning urinary bladder due to neurologic dysfunction and the symptoms depend on the site of neurological insult.
  - The effect on detrusor muscle:
    - Detrusor underactivity
    - Detrusor overactivity
  - The effect on urinary sphincter:
    - Sphincter underactivity
    - Sphincter overactivity and loss of coordination with bladder function.
- The management of children with neurogenic bladder sphincter dysfunction is similar irrespective of the underlying cause.
- The aim is:
  - Early diagnosis
  - Early medical treatment
  - To prevent the adverse effects on the bladder which subsequently will lead to incontinence and secondary damage to the kidneys.
- The management of NBSD in children has undergone major changes over the years.
  - One of the most important advancement was the introduction of clean intermittent catheterization (CIC).
  - The second important aspect of their management was the use of anticholinergics.
  - The third important breakthrough in their management is the wide use of urodynamic studies to diagnose these patients, classify their defect and institute early and proper treatment.
- CIC, combined with anticholinergics when necessary has made “conservative” management of children with NBSD a successful treatment option, with a good outcome in term of:
  - Quality of life of these children
  - Avoiding damage to the kidneys
- Urodynamic assessment is essential for the diagnosis and prognosis of pediatric neurogenic bladder.
- Urodynamic studies are functional studies of the lower urinary tract; they evaluate storage and emptying functions of the bladder.

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A.H. Al-Salem, *An Illustrated Guide to Pediatric Urology*, DOI 10.1007/978-3-319-44182-5_11

- Urodynamic studies can be simple and non-invasive (bladder diary and flow rate) or invasive (cystometrogram and videourodynamics).
- A cystometrogram measures the relationship between bladder filling and pressure. Parameters used to characterize the bladder are capacity, compliance, detrusor activity and sphincter activity.
- On the other hand, invasive urodynamic studies are indicated to evaluate and characterize the neuropathic bladder.
- Risk factors indicative of a poor prognosis include:
  - Reduced bladder capacity for age
  - Poor compliance
  - Elevated detrusor leak point pressure (>40 cm H_2O)
  - Features of functional bladder outlet obstruction on electromyography, such as detrusor sphincter dyssynergia.
- The urodynamic studies allows each child to be categorized into one of four subtypes of neuropathic bladder dysfunction based on sphincter and detrusor muscle activity. Although these categories may overlap, they assist in patient management.
  - Type A: Sphincter overactivity combined with detrusor underactivity
  - Type B: Sphincter overactivity combined with detrusor overactivity
  - Type C: Sphincter underactivity combined with detrusor underactivity
  - Type D: Sphincter underactivity combined with detrusor overactivity
- Despite the etiology, the principles for management are similar:
  - To insure and maintaining an adequate sized, normally compliant, urinary bladder
  - To evacuates urine completely, at a relatively low pressure
- Early diagnosis and treatment can prevent both renal damage and secondary bladder-wall changes, thereby improving long-term outcomes.
- Medical management with CIC and anticholinergics is effective in preserving renal function and providing safe urinary continence in more than 90 % of patients with a neurogenic bladder.

11.2 Physiology and Bladder Function

- The urinary bladder has two functions:
  - To store urine (A storage function)
  - To expel urine (A micturition function)
- Both of these functions are well coordinated and this coordinated function is regulated by the central and peripheral nervous systems.
- During the storage phase, the urinary bladder acts as a low-pressure reservoir, while the urinary sphincter maintains high resistance to urinary flow to keep the bladder outlet closed.
- During this phase, the pressure inside the urinary bladder remains low.
- This phase depends on:
  - The intrinsic viscoelastic properties of the bladder
  - Inhibition of the parasympathetic nerves
  - Sympathetic nerves also facilitate urine storage in the following ways:
    - Sympathetic nerves inhibit the parasympathetic nerves from triggering bladder contractions.
    - Sympathetic nerves directly cause relaxation and expansion of the detrusor muscle.
    - Sympathetic nerves close the bladder neck by constricting the internal urethral sphincter.
- During micturition, the urinary bladder contracts to expel urine while the urinary sphincter relaxes and opens to allow unobstructed urinary flow and bladder emptying.
- As the bladder fills, the pudendal nerve becomes excited.
- Stimulation of the pudendal nerve results in contraction of the external urethral sphincter.
- Contraction of the external sphincter, coupled with that of the internal sphincter, maintains

urethral pressure higher than normal bladder pressure.

- The combination of both urinary sphincters is known as the continence mechanism.
- The pressure gradients within the bladder and urethra play an important functional role in normal micturition.
- As long as the intraurethral pressure is higher than that of the intravesical, patients will remain continent.
- If the urethral pressure is abnormally low or if the intravesical pressure is abnormally high, urinary incontinence will result.
- The bladder and urethra are innervated by three sets of peripheral nerves arising from the autonomic nervous system (ANS) and somatic nervous system.
  - Autonomic nervous system
    - Parasympathetic (S2, S3, S4)
      - This is motor to detrusor muscles of urinary bladder
      - This is inhibitory to internal urethral sphincter
    - Sympathetic (T10 to L2)
      - This is motor to internal urethral sphincter
      - This is inhibitory to detrusor muscle of urinary bladder
  - Somatic nerve (S2, S3, S4)
    - Pudendal nerves
- Micturition is a spinal reflux facilitated and inhibited by higher brain center and subject to voluntary facilitation and inhibition.
- The brain is the master control of the entire urinary system and this is done through the micturition control center which is located in the frontal lobe of the brain.
- The micturition control center send inhibitory signals to the detrusor muscle of the urinary bladder to prevent the bladder from contracting and emptying until a socially acceptable time and place to urinate is available.
- The signal transmitted by the brain reach the urinary bladder through the brainstem and the sacral spinal cord.
- The pons part of the brainstem is responsible for coordinating the activities of the urinary sphincters and the bladder so that they work in synergy.
- This is done through the pontine micturition center (PMC).
- The PMC coordinates the urethral sphincter relaxation and detrusor contraction to facilitate urination.
- Stimulation of the PMC causes the urethral sphincters to open while facilitating the detrusor muscle to contract and expel the urine.
- The PMC is also affected by emotions, which is why some people may experience incontinence when they are excited or scared.
- The ability of the brain to control the PMC is part of the social training that children experience during growth and development.
- Usually the brain takes over the control of the pons at age 3–4 years, which is why most children undergo toilet training at this age.
- When the bladder becomes full, the stretch receptors of the detrusor muscle send a signal to the PMC, which in turn notifies the brain that there is a sudden desire to go to the bathroom and empty the urinary bladder.
- Under normal situations, the brain sends an inhibitory signal to the pons to inhibit the bladder from contracting until it is socially acceptable to micturate.
- When the PMC is deactivated, the urge to urinate disappears, allowing the patient to delay urination until finding a socially acceptable time and place.
- When urination is appropriate, the brain sends excitatory signals to the PMC, allowing the urinary sphincters to open and the detrusor muscle to contract and empty the urinary bladder.
- All these excitatory and inhibitory signals pass via the spinal cord (the sacral reflex center).
- The information (signals) from the urinary bladder travels up the spinal cord via the sacral cord to the PMC and then to the brain.

- The brain interprets this signal and sends a reply via the PMC that travels down the spinal cord to the sacral cord and, subsequently, to the urinary bladder.
- An intact spinal cord is critical for normal micturition.
- In the event of spinal cord injury, the patient will develop detrusor sphincter dyssynergia with detrusor hyperreflexia (DSD-DH). The patient will have urinary frequency, urgency, and urge incontinence but cannot empty the bladder completely.
- In infants, the spinal reflex center is responsible for controlling the act of micturition which happens involuntary once the bladder is full. When the bladder is full, an excitatory signal is sent to the sacral cord (the sacral reflex center) which automatically triggers the detrusor to contract leading to involuntary detrusor contractions and bladder emptying. This is temporary and once the higher center of voiding control (the brain) is mature enough it will control and command the bladder. Voluntary continence usually is attained by age 3–4 years.
- Another important component of the act of micturition is the autonomic nervous system which is divided into the sympathetic and the parasympathetic nervous system.
- Under normal conditions, the bladder and the internal urethral sphincter primarily are under sympathetic nervous system control. When the sympathetic nervous system is active:
  - It causes the bladder to relax and increase its capacity without increasing detrusor resting pressure
  - It stimulates the internal urinary sphincter to remain tightly closed.
  - It also inhibits parasympathetic stimulation
  - As a result the micturition reflex is inhibited

Effects of the Sympathetic System on the Urinary Bladder

- It causes bladder relaxation
- It stimulates the internal urinary sphincter to remain closed
- It inhibit the effect of the parasympathetic system
- The end result is inhibition of micturition

- The parasympathetic nervous system functions in a manner opposite to that of the sympathetic nervous system.
  - The parasympathetic nerves stimulate the detrusor to contract.
  - The sympathetic influence on the internal urethral sphincter becomes suppressed so that the internal sphincter relaxes and opens.
  - The activity of the pudendal nerve is inhibited and this causes the external urethral sphincter to open.
  - The end result is voluntary urination.

Effects of the Parasympathetic System on the Urinary Bladder

- It stimulates the detrusor muscles to contract
- It stimulates the internal urinary sphincter to relax and open by suppression of the sympathetic effect
- It inhibit the effect of the pudendal nerve which causes relaxation of the external urethral sphincter
- The end result is voluntary micturition

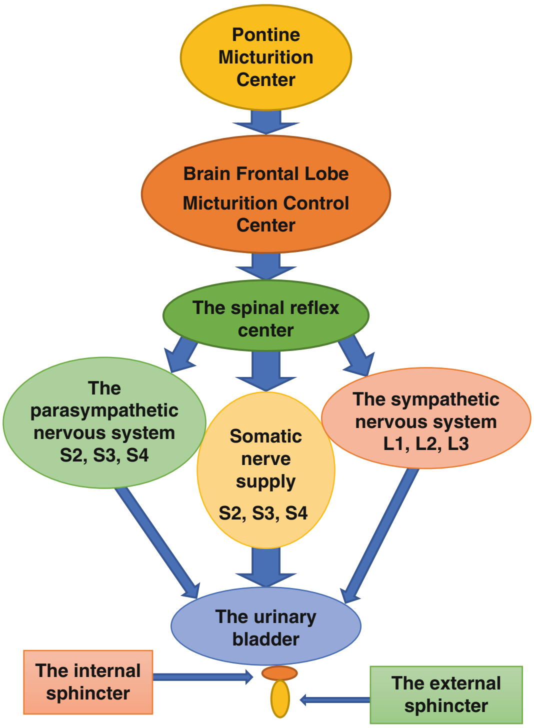
Somatic Nerve (S2, S3, S4) Supply to the Urinary Bladder

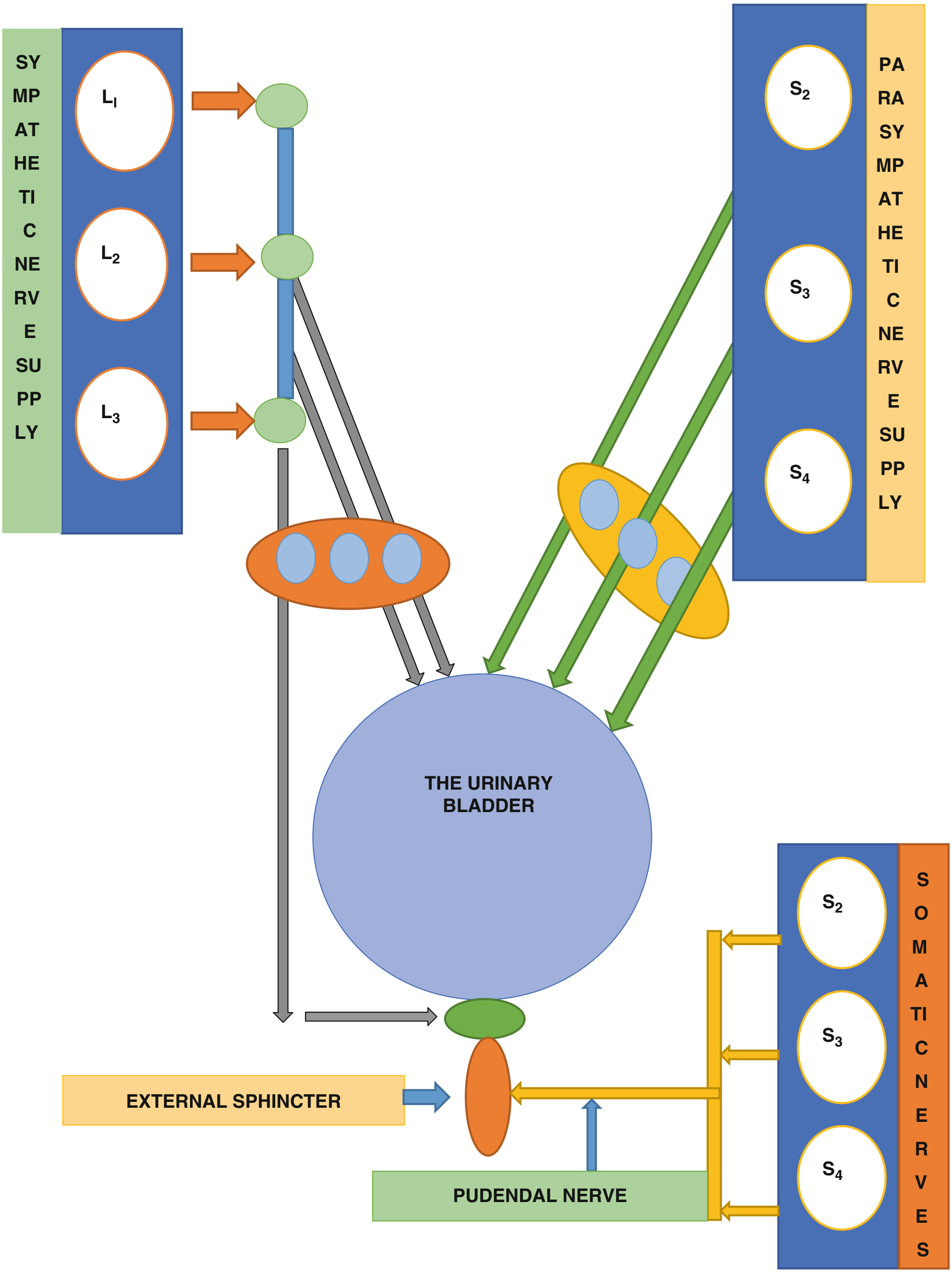
- Stimulation leads to contractions of the skeletal muscle fibers of the external urinary sphincter
- During micturition, this nerve is inhibited leading to relaxation of the external urinary sphincter which allows urination

Control of Urinary Bladder Function

- The storage function of the urinary bladder is enabled by:
  - Inhibition of detrusor muscles (sympathetic innervation)
  - Contraction of the striated external urinary sphincter (somatic innervation)
  - Contraction of smooth muscle internal sphincter (sympathetic innervation)
- The micturition function of the urinary bladder is enabled by:
  - Relaxation of the striated external sphincter (somatic innervation)
  - Relaxation of the smooth muscle internal sphincter and opening of the bladder neck (sympathetic innervation)
  - Detrusor muscle contraction (parasympathetic innervation)

- The somatic nervous system regulates the actions of the muscles under voluntary control. The pudendal nerve originates from the nucleus of Onuf and regulates the voluntary actions of the external urinary sphincter and the pelvic diaphragm.
  - Activation of the pudendal nerve causes contraction of the external sphincter and the pelvic floor muscles and prevent micturition.
  - Inhibition of the activity of the pudendal nerve causes the external urethral sphincter to relax and open to allow micturition


Pontine Micturition Center
Brain Frontal Lobe Micturition Control Center
The spinal reflex center
The parasympathetic nervous system S2, S3, S4
Somatic nerve supply S2, S3, S4
The sympathetic nervous system L1, L2, L3
The urinary bladder
The internal sphincter
The external sphincter


SYMPATHETIC NERVE SUPPLY
L1
L2
L3
PARASYMPATHETIC NERVE SUPPLY
S2
S3
S4
THE URINARY BLADDER
EXTERNAL SPHINCTER
PUDENDAL NERVE
SOMATIC NERVES
S2
S3
S4

11.2.1 Micturition

- Bladder function is automatic but completely governed by the brain, which makes the final decision on whether or not to void.
- The normal function of urination means that an individual has the ability to stop and start urination on command.
- In addition, the individual has the ability to delay urination until a socially acceptable time and place.
- When the bladder is filled to capacity, the stretch receptors within the bladder wall send signal to the spinal reflex center in the sacral cord. These signals indicate a need to void.
- The spinal reflex center send signals to the PMC which is, in turn, modulated by inhibitory and excitatory neurologic influences from the brain.
- When an individual cannot find a bathroom nearby, the brain bombards the PMC with a multitude of inhibitory signals to prevent detrusor contractions.
- At the same time, an individual may actively contract the levator muscles to keep the external sphincter closed or initiate distracting techniques to suppress urination.
- When micturition is socially acceptable, the brain sends excitatory signals to the PMC which in turn send signals to the sacral cord.
- The sacral cord, in turn, sends a message back to the bladder indicating that it is time to empty the bladder.
- At this point, the pudendal nerve causes relaxation of the levator ani so that the pelvic floor muscle relaxes.
- The pudendal nerve also signals the external urinary sphincter to relax and open.
- The sympathetic nerves send a message to the internal sphincter to relax and open, resulting in a lower urethral resistance.
- When the urethral sphincters relax and open, the parasympathetic nerves trigger contraction of the detrusor muscles.
- When the bladder contracts, the pressure generated by the bladder overcomes the urethral pressure, resulting in urinary flow.
- These coordinated series of events allow unimpeded, automatic emptying of the urine.
- A repetitious cycle of bladder filling and emptying occurs in newborn infants. The bladder empties as soon as it fills because the brain of an infant has not matured enough to regulate the urinary system. Because urination is unregulated by the infant's brain, predicting when the infant will urinate is difficult.
- As the infant brain develops, the PMC also matures and gradually assumes voiding control.
- When the infant enters childhood (usually at age 3–4 years), this primitive voiding reflex becomes suppressed and the brain dominates bladder function, which is why toilet training usually is successful at age 3–4 years.

11.3 Pathophysiological Changes of NBSD

- Under normal conditions, the detrusor muscle, bladder neck, and striated external sphincter function as a synergistic unit for adequate storage and complete evacuation of urine.
- In patients with NBSD, the bladder function is affected. This is as a result of disordered innervation of the detrusor musculature and external sphincter.
- Children with NBSD and based on intravesical pressure can be categorized into two groups:
  - High-risk group
  - Low-risk group
- This classification is important to predict secondary renal damage from a neurogenic bladder.
- In healthy bladders, the change in bladder-filling pressure between empty and full is normally less than 10–15 cm H_2O.
- Any pathophysiologic process that causes either intermittent or continuous elevation of intravesical pressure above 40 cm H_2O places the child at risk for:
  - Upper urinary tract dysfunction
  - Urinary tract infections
  - Renal failure

- As a result of increased intravesical pressure above 40 cm H_2O, the following changes will occur:
  - The glomerular filtration rate decreases
  - The pyelocaliceal and ureteral drainage deteriorates
  - Obstructive hydronephrosis and/or vesicoureteral reflux
- Even in the absence of vesicoureteral reflux or upper urinary tract dilatation, high intravesical pressure can impair drainage of urine into the bladder.
- Intermittent elevation of intravesical pressure may occur from:
  - Detrusor hypertonia
  - Hyperreflexia
  - Both
- Hyperreflexia may cause intermittent elevation of intravesical pressure, especially if the external sphincter remains tight rather than relaxes in an attempt to prevent micturition (detrusor sphincter dyssynergia).
- Over a long period of time, hyperreflexia with pressures exceeding 40 cm H_2O may result in:
  - Detrusor decompensation (areflexia from myogenic failure)
  - Detrusor hypertrophy with associated sacculations and subsequent diverticula formation.
  - Loss of the elastic and vesicoelastic properties of the bladder
  - Mechanical ureterovesical junction obstruction
- Continuous elevation of intravesical pressure above 40 cm H_2O may occur from a hypertonic detrusor or a hypertrophic small-capacity bladder secondary to outflow obstruction.
- Bladder outlet obstruction is caused by:
  - Detrusor sphincter dyssynergia
  - Fibrosis of the external urethral sphincter secondary to partial or complete denervation.
- Bladder outlet obstruction will lead to elevated voiding pressures, which will contribute to either detrusor decompensation or hypertrophy.
- It is also important to note that residual urine in the bladder is a cause of recurrent urinary tract infections and these may affect the urinary bladder leading to damage, inflammation and fibrosis of the urinary bladder.
- In children with NBSD, irreversible renal damage is caused by several factors:
  - High intravesical pressures
  - Vesicoureteral reflux
  - Lower urinary tract infections
  - Acute pyelonephritis

11.4 Etiology and Clinical Features

- Neurogenic bladder is a malfunctioning bladder secondary to neurologic disorders which can affect:
  - The brain
  - The pons
  - The spinal cord
  - The sacral cord
  - The peripheral nerves
- Detrusor hyperreflexia:
  - This refers to overactive bladder symptoms due to a suprapontine upper motor neuron neurologic disorder.
  - The external sphincter functions normally.
  - The detrusor muscle and the external sphincter function in synergy.
  - Detrusor hyperreflexia is characterized by the presence of involuntary detrusor contractions, usually at low volumes.
  - This can produce symptoms of urgency and urge incontinence.
  - The treatment is composed of anticholinergic medications to reduce contractions and timed voiding or use of CIC.
- Detrusor external sphincter dyssynergia (DSD):
  - There is increased sphincter activity during detrusor contraction.
  - DSD has been associated with an increased risk of upper GU tract deterioration in as many as 70 % of patients.
  - DSD is typically managed with CIC and anticholinergic medications.
- DSD-DH (detrusor sphincter dyssynergia with detrusor hyperreflexia):
  - This refers to overactive bladder symptoms due to neurologic upper motor neuron disorder of the suprasacral spinal cord.

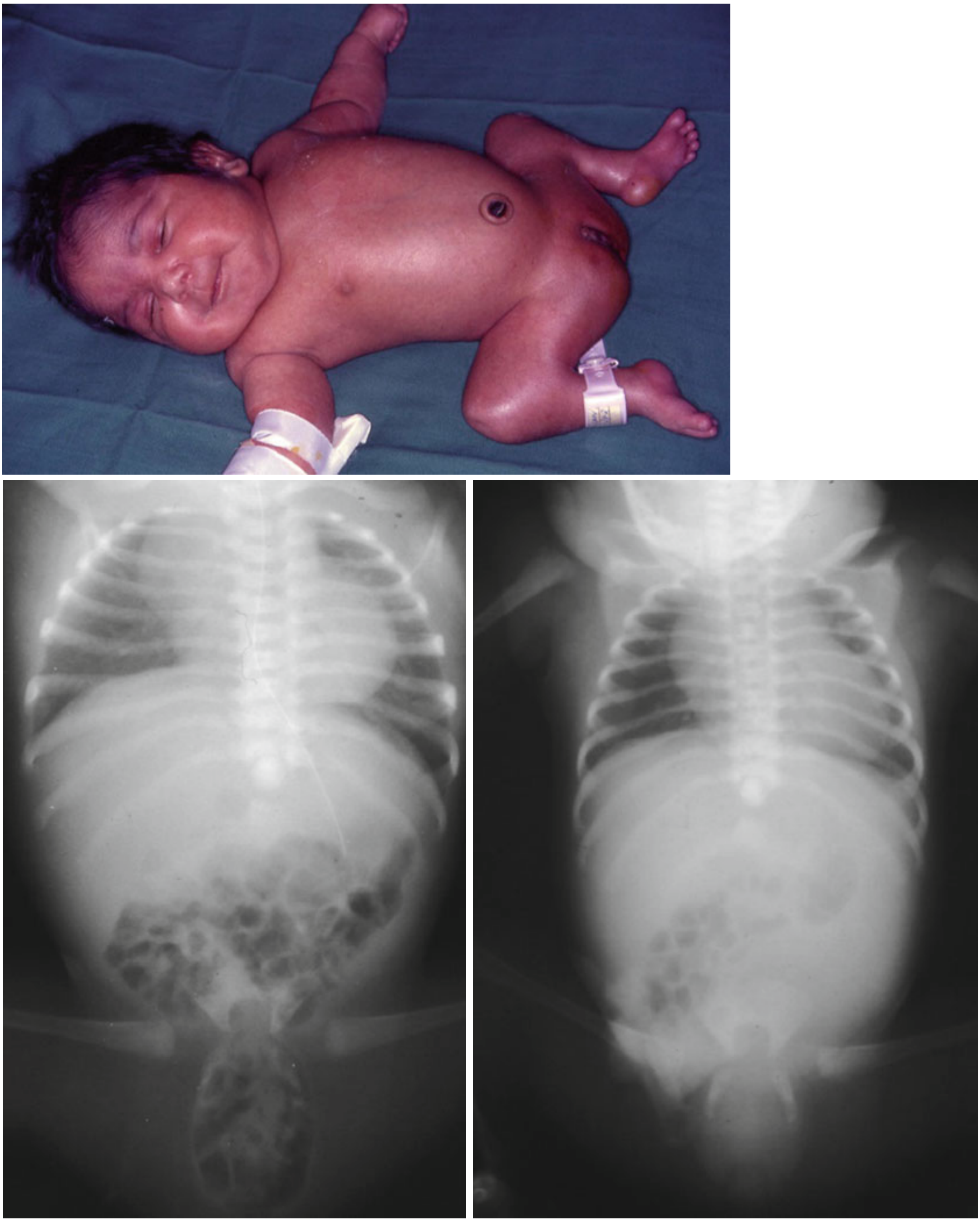
  - Both the detrusor and the sphincter are contracting at the same time; they are in dyssynergy (lack of coordination).
  - The patient will have urinary retention.
- Detrusor hyperreflexia with impaired contractility (DHIC):
  - This refers to overactive bladder symptoms, but the detrusor cannot generate enough pressure to allow complete bladder emptying.
  - The external sphincter is in synergy with detrusor contraction but the detrusor is too weak to mount an adequate contraction for proper voiding to occur.
  - The condition is similar to urinary retention, but irritating voiding symptoms are prevalent.
- Detrusor instability:
  - This refers to overactive bladder symptoms without neurologic impairment.
  - The external sphincter functions normally, in synergy.
- Overactive bladder:
  - This refers to symptoms of urinary urgency, with or without urge incontinence
  - It is usually associated with frequency and nocturia.
  - The cause may be neurologic or nonneurologic.
- Detrusor areflexia:
  - This refers to complete inability of the detrusor muscle to empty the urinary bladder due to a lower motor neuron lesion (e.g. sacral cord or peripheral nerves).
  - The bladder does not generate a contraction.
  - The result is that the bladder will not empty (stasis).
  - These patients can occasionally void with abdominal straining, but, except in rare cases, they need to be managed with clean intermittent catheterization (CIC).
- Outflow obstruction:
  - In patients with outflow obstruction, high voiding and/or storage pressures are seen.
  - This is associated with increased risk of upper urinary tract deterioration.
  - This is managed with CIC, surgical resection of the obstructing lesion, or urinary diversion in extreme cases.
- Urinary retention:
  - This refers to the inability of the urinary bladder to empty.
  - The cause may be neurologic or nonneurologic.
- The central nervous system is considered the master control of the urinary bladder function and lesions affecting this will affect the entire voiding cycle.
- Any part of the nervous system may be affected, including the brain, pons, spinal cord, sacral cord, and peripheral nerves.
- This will result in symptoms of dysfunctional voiding, ranging from acute urinary retention to an overactive bladder or to a combination of both.
  - Urinary incontinence results from a dysfunction of the bladder, the sphincter, or both.
  - Bladder overactivity (spastic bladder) is associated with the symptoms of urge incontinence.
  - Sphincter underactivity (decreased resistance) results in symptomatic stress incontinence.
  - A combination of detrusor overactivity and sphincter underactivity may result in mixed symptoms.
- Lesions of the brain above the pons affect the master micturition control center, causing a complete loss of voiding control.
  - The voiding reflexes of the lower urinary tract remain intact.
  - The clinical features include:
    - Urge incontinence
    - Spastic bladder (detrusor hyperreflexia or overactivity)
    - The bladder empties too quickly and too often, with relatively low quantities, and storing urine in the bladder is difficult.
    - These patients usually rush to the bathroom and even leak urine before reaching there.
    - They may wake up frequently at night to void.

  - The causes include:
    - Stroke
    - Brain tumors
    - Parkinson disease
    - Hydrocephalus
    - Cerebral palsy
    - Shy-Drager syndrome
- Diseases or injuries of the spinal cord between the pons and the sacral spinal cord also result in spastic bladder or overactive bladder.
  - Initially, after spinal cord trauma, there is a spinal shock where the nervous system shuts down. After 6–12 weeks, the nervous system reactivates.
  - When the nervous system becomes reactivated, it causes hyperstimulation of the urinary bladder.
    - These patients experience urge incontinence.
    - The bladder empties too quickly and too frequently.
    - If both the bladder and external sphincter become spastic at the same time, the patients will sense an overwhelming desire to urinate but only pass a small amount of urine (detrusor-sphincter dyssynergia) because the bladder and the external sphincter are not in synergy.
  - Children born with myelomeningocele may have spastic bladders and/or an open urethra or they may have a hypocontractile bladder instead of a spastic bladder.
- Sacral cord injury may prevent the bladder from emptying.
  - If a sensory neurogenic bladder is present, the affected patient may not be able to sense when the bladder is full.
  - In the case of a motor neurogenic bladder, the patient will sense the bladder is full and the detrusor may not contract, a condition known as detrusor areflexia.
  - These patients have difficulty eliminating urine and experience overflow incontinence; the bladder gradually overdistends until the urine spills out.
  - The causes of sacral diseases include:
    - Sacral cord tumors
    - Herniated disc
    - Traumatic
    - Lumbar laminectomy
    - Radical hysterectomy
    - Abdominoperineal resection
  - In children, a tethered cord is a cause of dysfunctional voiding symptoms.
- Peripheral neuropathy as seen in those with diabetes mellitus and AIDS is a cause of urinary retention.
  - This leads to silent, painless distention of the bladder.
  - These patients will have difficulty urinating.
  - They also may have a hypocontractile bladder.
  - Other diseases include:
    - Poliomyelitis
    - Guillain-Barré syndrome,
    - Severe herpes in the genitoanal area
    - Pernicious anemia
    - Tabes dorsalis
- The most common cause of neurogenic bladder dysfunction in children is neurospinal dysraphism.
- The most common presentation is at birth with myelodysplasia.
- The term myelodysplasia includes a group of developmental anomalies that result from defects in neural tube closure.
- Lesions may include:
  - Spina bifida occulta
  - Meningocele
  - Lipomyelomeningocele
  - Myelomeningocele
- Other causes of neurogenic dysfunction include:
  - Sacral agenesis
  - Tethered spinal cord associated with imperforate anus, cloacal malformations
  - Spinal cord injuries from sporting injuries and motor vehicle accidents
  - Central nervous system abnormalities include spastic diplegia (cerebral palsy) and learning disabilities, i.e. attention deficit hyperactivity disorder (ADHD) or attention deficit disorder (ADD).
- Myelomeningocele is by far the most common defect seen and the most detrimental.
- Myelomeningoceles account for 90 % of open spinal dysraphism.

- The overwhelming majority of myelomeningoceles are directed posteriorly, with most defects involving the lumbar vertebrae.
- A small number (approximately 5 %) of patients with myelomeningoceles do not have a neurogenic bladder.
- Congenital defects of spinal column formation that are not open defects are often termed spina bifida occulta.
- The lesions can be subtle, often with no obvious signs of motor or sensory denervation; however, in many patients, a cutaneous abnormality can be seen overlying the lower spine. This can vary from a dimple or a skin tag to a tuft of hair, a dermal vascular malformation, or an obvious subdermal lipoma.
- The frequency of abnormal lower urinary tract function in patients with spina bifida occulta has been reported to be as high as 40 %.
- Traumatic and neoplastic spinal lesions of the cord are less frequent in children.
- Additionally, different growth rates between the vertebral bodies and the elongating spinal cord can introduce a dynamic factor to the lesion. Scar tissue surrounding the cord at the site of meningocele closure can also tether the cord during growth.
- Sacral agenesis, defined as the absence of two or more lower vertebral bodies, is another defect that can produce voiding dysfunction
- Total or partial sacral agenesis is a rare congenital anomaly that involves absence of part or all of one or more sacral vertebrae.
- This anomaly can be part of the caudal regression syndrome and has to be considered in any child presenting with anorectal malformation (ARM).
- Cerebral palsy patients may also present with varying degrees of voiding dysfunction usually in the form of uninhibited bladder contractions, voiding dysfunction often due to spasticity of the pelvic floor and sphincter complex and wetting.
- Bladder sphincter dysfunction is poorly correlated with the type and spinal level of the neurological lesion.
- Myelomeningocele
  - The exposed spinal cord and its nerve roots, and tension on the spinal cord as the cord ‘rises up’ the canal with elongation of the fetus, contribute to a variable picture of neural injury to the lower urinary tract and lower extremities.
  - This is coupled with obstruction of the aqueduct to the fourth ventricle (Chiari malformation).
  - The main issue is whether or not the child has detrusor external urethral sphincter dyssynergy and whether the infant can empty the bladder completely at low pressure.
  - It is important to investigate these patient early including:
    - A renal and bladder ultrasound
    - A catheterized measurement of urine residual after voiding or leaking
    - Serum creatinine
    - A urodynamic study that incorporates both detrusor pressure measurements and urethral sphincter electromyography.
    - Voiding cystography is done when there is hydronephrosis and/or urodynamic studies indicate bladder outlet obstruction with either increased pressure at capacity or bladder sphincter dyssynergy.
    - The incidence of reflux when there is functional obstruction of the bladder outlet can range as high as 50 %.
  - The presence of the following factors which can result in upper urinary tract deterioration calls for early treatment with clean intermittent catheterization (CIC) and anticholinergic drugs:
    - Elevated detrusor filling pressure
    - Bladder sphincter dyssynergy
    - High voiding or leaking pressures (above 40 cm H_2O) at capacity
    - Reflux grade III or higher
  - Most clinicians now advocate full investigation of the lower urinary tract and initiate prophylactic treatment if there are signs of outlet obstruction and/or elevated bladder filling or voiding pressure.
  - This is to avoid urinary tract deterioration which can be greater than 50 % if a watch and wait policy is adopted.

  - There are several advantages of starting CIC and anticholinergic therapy in infancy.
    - The parents and the child adapt to the routine of CIC much easier than they would have if it were to be begun when the child is older
    - The bladder often remains very compliant, expanding as the child grows
    - The bladder maintain appropriate wall thickness
    - Hydronephrosis and vesicoureteral reflux develop in fewer than 10 %
    - Continence is readily achieved in greater than 50 % with no additional maneuvers
    - The need for augmentation cystoplasty is markedly reduced from almost 60–16 % when compared with that in children followed expectantly.
    - Reduced effect on renal function and renal scarring
  - When vesicoureteral reflux is present, CIC effectively lowers the intravesical emptying pressure.
  - Anticholinergics can be added to lower detrusor filling pressure, increasing compliance without fear of causing urinary retention when combined with CIC.
  - The lowered filling and emptying pressures has proven to be very beneficial.
  - In 30–50 % of children reflux is resolved within 2–3 years of its discovery and initiation of therapy.
  - The disadvantages include a higher rate of bacteriuria (60–70 % versus 30 % in those treated expectantly) but a lower rate of symptomatic urinary tract infection (20 % versus 40 % in those treated expectantly).
  - Credé voiding is to be avoided.
  - Several alpha sympathomimetic agents, such as phenylpropanolamine, ephedrine or pseudoephedrine, are used to increase bladder outlet resistance when it is not sufficient to maintain continence between CICs.
  - A variety of surgical procedures can be used in selected patients to lower intravesical pressure and increase bladder capacity and or increase bladder outlet resistance.
    - Bladder augmentation is the commonest procedure but this is not without complications including mucus production, recurrent urinary infection, electrolyte imbalance, stone formation and rarely the late occurrence of cancer in the augmented segment.
    - Surgeries to increase bladder outlet resistance include implantation of an artificial urinary sphincter, bladder neck tightening, using adjacent tissue, a fascial sling, and various bulking agents.
    - Creating a catheterizable urinary stoma in those children with intractable urethral incontinence or inability to catheterize their urethra easily.
- Occult spinal dysraphism:
  - The wide spread use of spinal ultrasound and MRI increased the detection and diagnosis of occult spinal dysraphism.
  - Occult spinal dysraphism is known to be associated with:
    - An intraspinal lipoma or lipomeningocele
    - A diastematomyelia
    - A fatty filum with tethering
    - A dermal sinus tract
    - A cutaneous lower midline back lesion is detected in 90 % of patients with occult spinal dysraphism
      - A subcutaneous mass
      - A dermal vascular malformation
      - Hypertrichosis
      - A midline dimple or sinus tract
      - A skin tag
      - An asymmetric gluteal cleft
    - Most infants have no other manifestation of this disease (other than the cutaneous lesion) but the neurologic lesion progress with advancing age.
    - Normally, the conus medullaris ends at L1, L2 at birth but ‘rises’ cephalad to T12, L1 at puberty.
    - The differential growth rate between the spinal cord and the vertebral bodies stretches the lower cord and cauda equina due to fixation of the filum terminale to the bottom of the vertebral canal, or the nerves roots emerging from the cord become compressed by an expanding intraspinal lipoma.

        - With time, this stretching and/or compression affects the oxidative process of the neural tissue that then leads to impaired function of the lower extremities and/or lower urinary tract.
        - These patients should be investigated including a renal and bladder ultrasound and a urodynamics study.
        - The findings of urodynamics studies in children less than 1 year old are invariably normal.
        - The most common findings in infancy are partial denervation of the urethral sphincter muscle or failure of the sphincter to relax during a detrusor contraction.
        - The most common findings in older children are extensive denervation of the sphincter and/or an acontractile detrusor combined with changes in lower extremity function.
        - A voiding cystourethrogram is indicated when the urodynamics parameters suggest risk to the upper urinary tract from increased bladder outlet resistance or poor detrusor compliance.
        - Vesicoureteral reflux, hydronephrosis and urinary incontinence are all managed similar to those with myelomeningocele.
        - The abnormal neurological effects can improve following spinal cord de-tethering when performed in infant, but this is unlikely when performed in older children.
- Sacral agenesis:
    - This is defined as partial or complete absence of the lowermost vertebral bodies.
    - Sacral agenesis can range from absence of just the last two or three sacral bodies to the absence of sacral and several lumbar bones as well (sirenomyelia) (Figs. 11.1, 11.2, and 11.3).
    - This can be seen:
        - In offspring of insulin-dependent diabetic mothers (1 %)
        - As part of a genetic disorder due to a deletion of part of chromosome 7 (7q36) (HLXB9 genetic mutations).
        - In familial cases of sacral agenesis associated with the Currarino triad syndrome (presacral mass, sacral agenesis and anorectal malformation).
        - Sacral agenesis may represent one point on a spectrum of abnormalities that encompass a sacral meningocele and ano-rectal malformations.
    - In the newborn period these infants appear normal and the pathognomic sign is absence of the upper end of the gluteal cleft, with flattened buttocks.
    - When the diagnosis is considered a lateral spine film or a spinal ultrasound in infants will confirm the abnormality.
    - A spinal MR reveals a sharp cut off to the cord at about T-12, with nerve roots streaming from it.
    - Approximately 90 % of children develop neurogenic bladder dysfunction.
    - These patients may have:
        - An overactive detrusor with sphincter dyssynergy leading to recurrent urinary tract infection and vesicoureteral reflux
        - Or an acontractile detrusor with complete denervation in the urethral sphincter leading to continuous incontinence.
    - The management depends on the type of neurogenic dysfunction.
        - CIC, anticholinergics and antibiotics are indicated in those with an upper motor neuron type lesion
        - Surgical interventions with CIC are indicated in those with an incompetent sphincter mechanism.
- Cerebral palsy:
    - This results from a non-progressive injury to the brain, occurring in the perinatal period, commonly following a period of brain hypoxia or infection.
    - The incidence of cerebral palsy is increasing, as more severely premature infants are surviving.
    - Cerebral palsy produces a neuromuscular disability or complex of cerebral dysfunction symptoms.
    - It is commonly seen:
        - In prematures who are less than 2 kg at birth



Figs. 11.1, 11.2, and 11.3 Clinical and radiological pictures of a patient with caudal regression syndrome

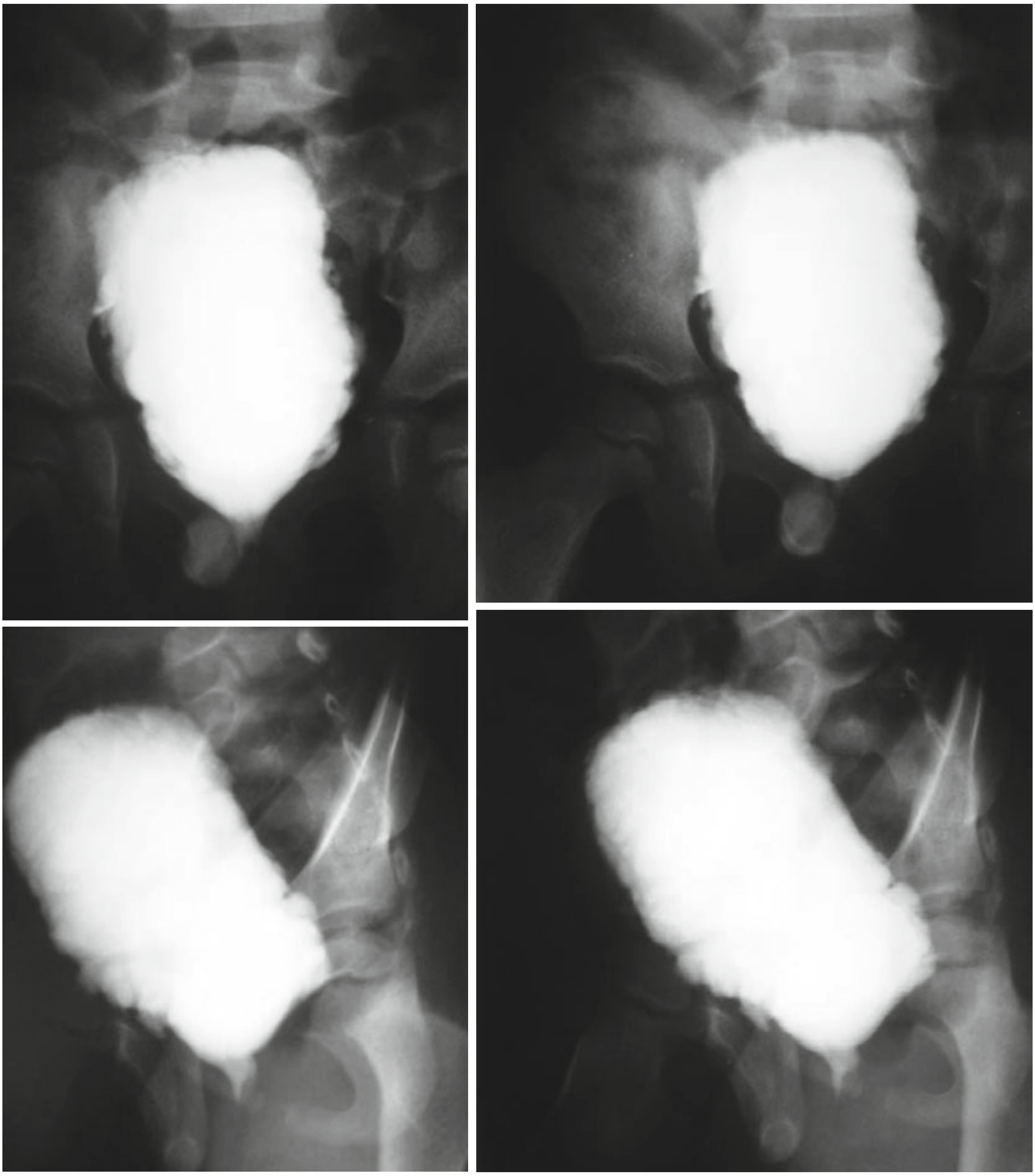
- In newborns following intraventricular hemorrhage
- In newborns who experienced a neonatal seizure
- In newborns who received mechanical ventilation for a prolonged period of time
  - Most children with cerebral palsy develop total urinary control.
  - Incontinence is seen in approximately 24 % of affected children. This may be related to the physical handicap rather than true incontinence.

  - Children with cerebral palsy rarely develop urinary tract infection and vesicoureteral reflux and their kidneys are usually normal on ultrasound.
  - In cerebral palsy, an upper motor neuron lesion leads to bladder dysfunction with detrusor overactivity (80 %), but not necessarily with detrusor sphincter dyssynergy (5 %)
  - On the other hand, a lower motor neuron lesion with sphincter denervation due to spinal cord involvement can be seen as well (11 %).
  - These patients have some ability to prevent leaking from an overactive detrusor by tightening the muscle for a variable period of time.
  - Children with milder forms of cerebral palsy dysfunction, with just learning disabilities without spasticity, have an overactive detrusor. This is often associated with either urgency (with or without incontinence) and nocturia, or day and night wetting.
  - Anticholinergics are valuable for these patients and it is the treatment of choice. These must be monitored to prevent the development of retention.
- Traumatic injuries to the spine
  - These are rare and more commonly seen in boys than girls and the frequency increases with age.
  - It occurs as a result of:
    - A motor vehicle accident
    - A bicycle accident
    - A fall from a high place
    - A gunshot wound
    - A sport accident
    - Iatrogenically after surgery to correct scoliosis, kyphosis or other intraspinal lesions, congenital aortic anomalies, or patent ductus arteriosus operations
    - A hyperextension injury during high forceps delivery
  - The lower urinary tract dysfunction that ensues is not likely to be an isolated event but is usually associated with loss of sensation and paralysis of the lower limbs.
  - In children, radiologic investigation of the spine may not reveal any bony abnormality. This condition has been labeled SCIWORA (*s*pinal *c*ord *i*njury *w*ith*o*ut *r*adiologic *a*bnormality).
  - In children, this injury may be a transient event and although sensation and motor function of the lower extremities may be restored relatively quickly, the dysfunction involving the bladder and rectum may persist considerably longer.
  - During the acute phase of the injury:
    - The bladder is often acontractile and the urethral sphincter nonreactive, although normal-appearing bioelectric potentials can be recorded on sphincter EMG (spinal shock).
    - Over a variable but unpredictable period of time, detrusor contractility and sphincter reactivity return as spinal cord edema subsides.
    - With this return of function, an overactive detrusor and bladder-sphincter dyssynergy may develop if the lateral reticulospinal cord pathways to and from the brainstem have been disrupted.
    - When the lesion affects the cauda equina, there is probably little to no return of bladder or sphincter function.
  - Over time, the urodynamic pattern in patients with a thoracic-level lesion is:
    - An overactive detrusor with sphincter dyssynergy
    - High voiding pressures
    - Eventual hydronephrosis and vesicoureteral reflux
  - Patients with an upper thoracic or cervical lesion are likely to exhibit autonomic dysreflexia with a spontaneous discharge of $\alpha 1$ stimulants during bladder filling and with contractions of the detrusor that require careful monitoring of their blood pressure during any investigational studies of the lower urinary tract.
  - The early management consist of:
    - Foley catheter insertion to drain the urinary bladder
    - CIC should be begun as soon as feasible and this should be tapered and stopped when the residual urines become insignificant (<5 ml)

  - Urodynamics studies should be performed no earlier than 6 weeks after the injury, to allow stabilization of the extent of the neurologic injury
  - Renal ultrasonography should be part of the assessment
  - Voiding cystography is done in those with signs of potential risk (i.e. sphincter dyssynergy or poor detrusor compliance).
  - The aim is to achieve low detrusor filling and voiding pressures with complete emptying and in the absence of this, these patients should continue on CIC in addition to anticholinergics.

11.5 Investigations and Diagnosis

- Urinalysis, and urine culture
- Serum electrolytes, BUN and creatinine levels
- Abdominal ultrasonography
- Lateral spine radiography is important to look for vertebral anomalies especially sacral agenesis.
- Magnetic resonance imaging
- Voiding cystourethrography (Figs. 11.4, 11.5, 11.6, and 11.7):
  - A voiding cystourethrogram can assess bladder neck and urethral function (internal and external sphincter) during filling and voiding phases.
  - A voiding cystourethrogram can identify a urethral diverticulum, urethral obstruction, and vesicoureteral reflux.
- Ultrasonography of the spinal canal can be useful in infants younger than 5 months; however, once the vertebrae begin to ossify, ultrasonography becomes much less sensitive.
- Measure of residual urine:
  - The postvoid residual urine (PVR) measurement is important.
  - If the PVR is high, the bladder may be acontractile or the bladder outlet may be obstructed.
  - Both of these conditions will cause urinary retention with overflow incontinence.
- Uroflow rate:
  - Uroflow rate is volume of urine voided per unit of time.
  - It is used to evaluate bladder outlet obstruction.
  - Low uroflow rate may reflect urethral obstruction, a weak detrusor, or a combination of both.
  - This test alone cannot distinguish an obstruction from a contractile detrusor.
- Urodynamic studies are essential for the diagnosis and management of children with neurogenic bladder.
- It is important to determine several urodynamic parameters, including:
  - Bladder capacity
  - Bladder compliance
  - Intravesical-filling pressure
  - Intravesical pressure at the moment of urethral leakage
  - Presence or absence of reflex
  - Detrusor activity
  - Competence of the internal and external sphincteric mechanisms
  - Degree of coordination of the detrusor and sphincteric mechanisms
  - Voiding pattern
  - Postvoiding residual urine volume
  - Detrusor and abdominal storage
  - Voiding pressures
  - Urine flow rate
  - Postvoiding residual volume
  - The relationship between detrusor contraction and the urinary sphincter
  - If contrast is instilled in the bladder, the anatomy can be imaged during voiding
- A urodynamic study consists of the followings:
  - The child is catheterized with a triple-lumen urodynamic catheter after lubricating the urethra with 1 % liquid lidocaine.
  - The intravesical pressure is recorded first.
  - The bladder is drained and the residual urine carefully measured and the residual volume pressure is determined.
  - This helps determine detrusor compliance at natural filling and is more accurate than cystometric compliance measured during even slow filling of the bladder.



Figs. 11.4, 11.5, 11.6, and 11.7 Micturating cystourethrograms showing neurogenic bladder

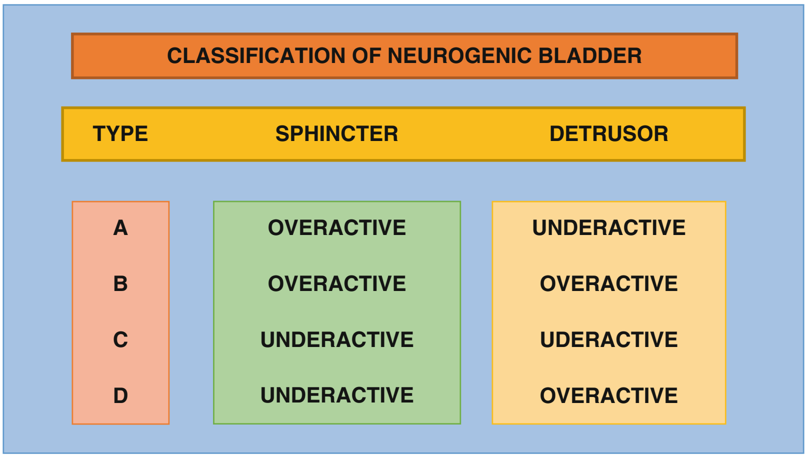
- A small balloon catheter is passed into the rectum to measure intra-abdominal pressure during the filling and emptying phases of the study.
- The side-hole port of the urethral pressure channel is positioned at the highest point of resistance in the urethra and kept in place.
- This measures resistance throughout bladder filling and emptying to determine the leak point pressure.
- External urethral sphincter electromyography (EMG) is performed using a 24-gauge concentric needle electrode inserted perineally in boys or para-urethrally in girls and advanced into the skeletal muscle component of the sphincter until individual motor unit action potentials are seen or heard on a standard EMG recorder.
- The characteristics of the individual motor unit potentials at rest, in response to various

  sacral reflexes (i.e. bulbocavernosus, anocutaneous, Valsalva and Credé maneuvers) and bladder filling and emptying are recorded to detect degrees of denervation.
  - Next, the bladder is filled through the second port while intravesical pressure is monitored via the third port of the tri-lumen urodynamic catheter.
  - The rate of bladder filling is set at 10 % of expected capacity for age.
  - The expected bladder capacity in milliliters = age (in years) +30 × 30.
  - Detrusor pressure measurements are continuously recorded throughout filling to calculate compliance, and during voiding or leaking to denote emptying pressure.
  - Detrusor overactivity:
    - This is defined as any short-lived pressure rise of >15 cm H_2O from baseline before capacity is reached.
  - Sometimes, the urodynamics study is combined with fluoroscopic video-imaging using a dilute radio-opaque contrast agent to visualize the appearance of the bladder wall and bladder neck or to detect the presence of vesicoureteral reflux during the test.
  - Alternatively, a radionuclide agent is instilled, with the patient lying above a nuclear camera, to determine at what pressure reflux occurs, when it is known to be present beforehand.
  - The study is not considered complete until the child actually urinates or leaks and the ‘voiding’ pressure is measured.
  - The small size of the urodynamic catheter does not seem to affect the voiding pressure adversely, even in very young children.
  - The normal end filling pressure should be <10 cm H_2O, while the normal voiding pressure varies from 55 to 80 cm H_2O in boys and from 30 to 65 cm H_2O in girls.
  - Urodynamic assessment can provide reproducible results in newborns and infants, but it requires attention to mechanical factors and filling rates.
- The main urodynamic study is cystometrography (CMG).
  - A small catheter is placed in the bladder, and the bladder is slowly filled with liquid.
  - Pressures within the bladder (intravesical) and the abdominal compartment are measured, and by subtracting the abdominal pressure from the intravesical pressure, the pressure generated by the detrusor muscle can be calculated.
  - Because the child is monitored through a filling and voiding phase, bladder capacity can be quantified, and the urine flow rate, postvoiding residual volume, and the force generated by a bladder contraction can be measured.
  - A filling cystometrogram assesses the bladder capacity, compliance, and the presence of phasic contractions (detrusor instability).
  - A voiding cystometrogram (pressure-flow study) simultaneously records the voiding detrusor pressure and the rate of urinary flow. This is the only test able to assess bladder contractility and the extent of a bladder outlet obstruction.
- Electromyography
  - If more information is desired, electromyography (EMG) can be used to demonstrate the relationship between the detrusor muscle and the external urinary sphincter.
  - Electromyography (EMG) helps to ascertain the presence of coordinated or uncoordinated voiding. Failure of urethral relaxation during bladder contraction results in uncoordinated voiding (detrusor sphincter dyssynergia). During normal voiding, the sphincter relaxes as the detrusor muscle contracts to allow unobstructed urinary flow.
  - Spinal cord injury can lead to discoordination so that the sphincter is closed when the detrusor contracts, creating high pressures within the bladder but low flow rates.
  - This is known as detrusor-sphincter dyssynergy (DSD).
  - EMG allows accurate diagnosis of detrusor sphincter dyssynergia common in spinal cord injuries
  - In infants with DSD, increased EMG activity occurs during voiding.
  - The presence of DSD places infants at a much greater risk of upper urinary tract deterioration.

- Fluoroscopy
  - Fluoroscopy can be used to perform video-urodynamic imaging with contrast enhancement of the bladder, which allows the bladder to be depicted during voiding.
  - In addition, reflux may be identified.
  - If a closed sphincter is revealed during voiding, this finding strongly suggest the presence of DSD, often obviating the need for EMG studies.
- Videourodynamics
  - Videourodynamics is important for evaluation of a patient with incontinence.
  - Videourodynamics combines the radiographic findings of voiding cystourethrogram (VCUG) and multichannel urodynamics.
  - Videourodynamics enables documentation of lower urinary tract anatomy, such as vesicoureteral reflux and bladder diverticulum, as well as the functional pressure-flow relationship between the bladder and the urethra.
- The urodynamics examination findings are considered normal when there is:
  - An appropriate capacity
  - A good compliant bladder
  - No overactivity
  - Normal innervation of the sphincter with normal sacral reflexes
  - An increase in sphincter activity during filling and complete silencing during emptying.
- An upper motor neuron lesion is present when there is:
  - Detrusor overactivity
  - And/or hyperactive EMG responses to sacral reflexes
  - And/or a failure of the sphincter muscle, on EMG, to relax (either partially or completely) with a bladder contraction or leaking at capacity.
- A lower motor neuron lesion is present when there are:
  - No contractions of the detrusor muscle
  - And/or there is a degree of denervation, either partial or complete, in the sphincter muscle, with characteristic EMG changes in the motor units or no motor unit activity at all, respectively
  - And little or no response in the sphincter to sacral reflexes and/or bladder filling or emptying.

11.6 Classification of Neurogenic Bladder

- There are various systems of classification of neurogenic bladder.
- Urodynamic and functional classifications have been more practical for defining the extent of the pathology and planning treatment in children.
- The main classification of neurogenic bladder is that based on urodynamic findings.
- The bladder and sphincter are two units working in harmony to make a single functional unit.
- The initial approach should be to evaluate the state of each unit and define the pattern of bladder dysfunction.
- This depends on the nature of the neurological deficit:
  - The bladder may be overactive with increased contractions, low capacity and compliance or inactive with no effective contractions.
  - The outlet sphincter may be independently overactive causing functional obstruction or paralyzed with no resistance to urinary flow.
  - These conditions may present in different combinations.
- This is important to plan a rational treatment for each individual patient.
- Urodynamic Studies are important to evaluate the lower urinary tract function and its deviations from normal.
- Since the treatment plan mainly depends upon a good understanding of the underlying problem in the lower urinary tract, a well performed urodynamic study is mandatory in the evaluation of each child with neurogenic bladder.
- A urodynamic study is also important to assess the response of the vesicourethral unit to therapy.
- In meningomyelocoele, most patients will present with hyperreflexive detrusor and dyssynergic sphincter, which is a dangerous combination as pressure is built up and the upper urinary tract is threatened.



CLASSIFICATION OF NEUROGENIC BLADDER

TYPE	SPHINCTER	DETRUSOR
A	OVERACTIVE	UNDERACTIVE
B	OVERACTIVE	OVERACTIVE
C	UNDERACTIVE	UDERACTIVE
D	UNDERACTIVE	OVERACTIVE

11.7 Management

- Bladder dysfunction is a general term used to describe abnormalities in either the filling and/or emptying of the bladder.
- It is a common problem in children and constitutes up to 40 % of pediatric urology clinic visits.
- Early identification and treatment of children at high risk of urinary dysfunctions is important in order to protect renal function and avoid urinary incontinence.
- During normal bladder function, acetylcholine released from parasympathetic nerves activates muscarinic receptors in the bladder which result in detrusor contraction and micturition.
- There are five subtypes (M1–M5) of muscarinic receptors expressed in the bladder. Of these, M2 receptors are the most abundant, although M3 receptors are more functionally active.
- In patients with a neuropathic bladder, disordered innervation commonly results in dyssynergia between the detrusor and external sphincters, which adversely affects bladder function.
- Oral anticholinergics, such as oxybutynin, block these receptors, causing relaxation of the bladder's smooth muscle, and are well established as the first line pharmacotherapeutic agents to treat neurogenic bladder.
- Anticholinergic drugs are useful to treat the neurogenic detrusor overactivity associated with types B and D bladder dysfunction by improving functional capacity and reducing filling pressures.
- Types A and C bladder dysfunctions usually require clean intermittent catheterisation alone, with marginal benefit expected from anticholinergics.
- The majority of children with neurogenic bladder (70–90 %) are effectively managed with oral anticholinergics and clean intermittent catheterization, avoiding the need for surgical intervention, e.g. augmentation cystoplasty or bladder outlet surgery.
- Side-effects of anticholinergic agents include:
  - Dry mouth
  - Blurred vision
  - Constipation
  - Facial flushing
  - Dizziness
- Clean intermittent catheterization is a safe and effective method of completely emptying the bladder, improving or eliminating urinary incontinence, reducing UTIs and protecting (along with anticholinergics) kidney function. Clean intermittent catheterization should be done three-hourly.
- The Credé maneuver (manual suprapubic pressure to expel urine) is discouraged.
- Surgical options for failure of conservative treatment include augmentation cystoplasty,

which increases bladder capacity and reduces pressure.

- The goals of management are:
  - To prevent or minimize secondary damage to the upper urinary tracts and bladder from the primary neurogenic bladder dysfunction
  - To achieve safe social continence
- The optimal management of neurogenic bladder involves:
  - Early diagnosis
  - Identifying high-risk groups
  - Institution of adequate treatment
  - Creating a low-pressure bladder reservoir
  - Ensuring complete and safe bladder emptying
- Early proactive treatment of high-pressure dyssynergic lower urinary tracts is important in the long term, not only to preserve renal function but also to prevent poor bladder compliance and the subsequent need for bladder augmentation.
- Without proper management, urinary tract infections and elevated bladder pressures with secondary bladder-wall changes may cause upper urinary tract deterioration within 3 years in up to 58 % of patients.
- Urodynamic assessment has become an integral part of the initial evaluation and subsequent management of children with neurogenic bladder.
  - It allows recognition of the different subtypes of NBSD
  - It allows the prediction of which newborns are at risk for upper urinary tract deterioration
  - It allows proactive interventions
  - It allows evaluation and guidance of therapy
  - It allows early detection of neurologic deterioration
  - This will minimize the deleterious effects of high intravesical pressure by directly measuring it rather than indirectly suspecting it from the development of upper and lower urinary tract changes on serial radiologic imaging.
  - Urodynamic risk factors are:
    - Low bladder compliance
    - Intravesical pressure more than 40 cm H_2O
    - DSD
- Others advocate selective urodynamic studies and depend on serial radiologic imaging to detect secondary evidence of high bladder pressure. They advocate prompt intervention at first signs of deterioration They reserve urodynamic studies only for patients with evidence of urinary retention on physical examination, new-onset hydronephrosis or febrile urinary tract infection, or for evaluation to achieve continence.
- Urodynamic assessment is important to classify NBSD.
- This allows presymptomatic interventions in the high-risk groups and plan treatment according to the type of dysfunction.
- The management must start before consequences of bladder dysfunction become apparent.
- Clean intermittent catheterization (CIC) or clean intermittent self-catheterization (CISC) in combination with anticholinergics (oxybutynin) is the standard therapy for children with neurogenic bladder dysfunction with detrusor hyperactivity and/or DSD.
  - CIC enables complete bladder emptying and thus avoids bladder residues and consequent risks for infections.
  - In the high-risk bladder with DSD, CIC also allows bladder emptying before the occurrence of otherwise “spontaneous” high-pressure voiding, which is known to be detrimental for kidney function and drainage.
- Oxybutynin, a bladder smooth-muscle relaxant, is used to improve bladder dynamics through suppression of detrusor hypertonicity and hyperreflexia.
  - Oxybutynin eliminates (high-pressure) uninhibited detrusor contractions (and thus urinary leakage)
  - Prevents high-pressure bladder storage (due to detrusor hypertonicity or low bladder compliance) and high-pressure emptying (in case of DSD).
- In clinical practice, four major subtypes can be used to describe NBSD.
  - Type A: Sphincter overactivity combined with detrusor underactivity
  - Type B: Sphincter overactivity combined with detrusor overactivity

  - Type C: Sphincter underactivity combined with detrusor underactivity
  - Type D: Sphincter underactivity combined with detrusor overactivity
- Dysfunctional type A:
  - This is the easiest type to treat.
  - The bladder requires early treatment because of urine retention with high filling pressure and continuous leaking.
  - CIC alone is effective and sufficient and will make the bladder safe and infection free, and the patient will be dry in between (social continence).
  - Good care to empty the bladder totally is most important to avoid bladder infections caused by residual urine.
- Dysfunctional type B:
  - This will have high filling and high voiding pressures.
  - It is very unsafe from birth onward due to DSD.
  - With oxybutynin, the overactive detrusor can be "pharmacologically converted" to an inactive reservoir (situation similar to type A), which has to be emptied with CIC.
- Dysfunctional type C:
  - CIC reduces the degree of incontinence and offers much better control over urinary tract infections.
  - To achieve continence, this type will at a later age need surgical intervention on the sphincter (e.g. sling operation).
  - An important point is that detrusor instability may emerge only after surgical improvement of outlet resistance. If this detrusor instability would remain unrecognized and untreated (with oxybutynin), bladder-outlet surgery would have converted a "wet but safe" into a "dry but unsafe" bladder.
- Dysfunctional type D:
  - The bladder leaks due to detrusor instability and gradually becomes unsafe due to secondary bladder-wall changes with detrusor hypertrophy and loss of bladder compliance.
  - Therefore, treatment consists of CIC combined with oxybutynin and, at a later age, bladder-outlet surgery.
- Treatment efficacy can be assessed using clinical parameters (including CIC frequency and volume charts), urinalysis, renal and bladder ultrasound, cystography, and video urodynamics.
- The long-term sequelae of insufficiently treated neurogenic bladders include renal scarring, and noncompliant fibrotic bladder. To avoid these changes, it is important to follow these patients closely:
  - 3× yearly up to age 3 years
  - 2× yearly in school-aged children
  - Yearly in adults
- The follow-up should include:
  - Urinalysis and culture
  - Renal and pelvic ultrasound
  - Cystography to investigate unexpected upper urinary tract infections
  - Urodynamics periodically to verify the effect of treatment
  - Modalities used to look at renal functions include nuclear imaging [dimercaptosuccinate acid (DMSA) renal scan], urinary concentrating ability, and glomerular filtration rate assessment.
- With early instituted and optimal treatment, the large majority of patients can be adequately controlled without antireflux surgery or surgical bladder augmentation.
- Augmentation cystoplasty is limited to a small group of patients in whom medical treatment fails (persistence of high filling pressures).
- In patients with insufficient sphincter activity, continence achievement will require bladder-outlet surgery in addition to medical treatment.
- Surgical intervention to provide a continent stoma will facilitate self-catheterization.

11.8 Clean Intermittent Catheterization

- In children with neurogenic bladder, CIC is the first-choice treatment to empty the bladder adequately (no residue, no infection) and safely (prior to high-pressure voiding), and it is a valuable tool for achieving continence.

- The wide variety of used materials and techniques for CIC does not seem to affect efficacy and safety as long as some basic principles are applied:
  - Proper education and training
  - Clean and atraumatic application
  - Achievement of good patient compliance on a long-term basis.
- For education, training, and further guidance during follow-up, a dedicated continence nurse is invaluable.
- CIC has been successfully used by parents even in newborns and infants, becoming a part of their everyday routine.
- Some authors prefer early institution of CIC in all infants with NBSD, given the fact that by the age of 3 years, CIC will be required in all for achieving continence, and given the difficulties of starting CIC at toddler age. Such early institution of CIC seems to improve family compliance and their ability to assist the child in coping with their disease and with CIC.
- CIC can be successfully taught to boys and girls who are motivated and who have developed the required dexterity, mostly around the age of 6 years.
- The required frequency of catheterization depends on several factors: fluid intake, bladder capacity, and bladder filling/voiding pressures.
- In practice, it is recommended to catheterize six times a day in infants (linked with feeding time) and five times a day in school-aged children.
- Although reported incidences of CIC-related infection risks are variable, it is generally agreed that the risk is low as long as complete bladder emptying is achieved. Furthermore, reused supplies are not related to more urinary tract infections. If symptomatic infections occur, these are mainly caused by incomplete bladder emptying, and CIC appliance by child or caregiver needs to be optimized.
- To prevent urethral strictures and false passage in boys, catheter lubrication and avoidance of forceful manipulation during catheter insertion are advocated.
- Neurogenic bowel dysfunction with constipation and fecal soiling can interfere with the institution of a successful CIC treatment. Retained stools may mechanically impair bladder filling, increase detrusor irritability, or contribute to urine retention. Stool incontinence increases the risk of bladder contamination and urinary tract infection. An effective bowel management program is therefore needed.
- Finally, given the high prevalence of latex allergy, in the spina bifida population, a strict latex-free approach is of extreme importance.

11.9 Anticholinergics

- Oxybutynin:
  - Of the anticholinergic agents available, oxybutynin hydrochloride is most commonly used, and long-term experience supports its safety also in newborns and infants.
  - Oxybutynin is a tertiary amine with a well-documented therapeutic effect on detrusor hyperactivity, and its effectiveness is attributed to a combination of anticholinergic (M3-selective receptor subtype antagonism), antispasmodic, local anesthetic and calcium-channel-blocking activity.
  - It provides a local anesthetic effect on irritable bladder and direct smooth muscle relaxant effect on urinary bladder.
  - Urodynamic studies have shown oxybutynin increases bladder size, decreases frequency of symptoms, reduces incontinence and delays initial desire to void.
  - Several studies have shown its efficacy for decreasing the filling pressure, increasing the capacity of the neurogenic bladder, and preserving renal function.
  - Extended-release oxybutynin is also available.
  - Transcutaneous extended-release oxybutynin has been shown to be well tolerated, with few undesired anticholinergic side-effects, apart from some skin reactions.
  - Furthermore, new-generation anticholinergic agents, such as darifenacin and solife-

  nacin, are selective for the M3 receptor and thus offer the potential of reduced side-effects.
  - Intravesical oxybutynin was shown to have increased efficacy and reduced side effects. Compared with oral oxybutynin, intravesical oxybutynin has more potent and longer-acting detrusor suppressive effects with good tolerance and should be used prior to considering surgical therapies.
  - The usual dose regimen of oral oxybutynin is 0.3–0.6 mg/kg per day in three doses.
  - In children with insufficient response or significant systemic side effects to oral oxybutynin, intravesical instillation of oxybutynin has been shown to be a highly efficacious, reliable, and well-tolerated therapy for children who would otherwise require surgical therapy.
  - Intravesical oxybutynin is used in dosages between 0.3 and 0.6 mg/kg per day in two or three doses. Given its better tolerability compared with oral treatment, if required, intravesical dosages can be further increased up to doses of 0.9 mg/kg per day.
- Tolterodine L-tartrate (Detrol and Detrol LA):
  - Tolterodine L-tartrate is a competitive muscarinic receptor antagonist for overactive bladder.
  - It differs from other anticholinergic types in that it has selectivity for urinary bladder over salivary glands.
  - It exhibits high specificity for muscarinic receptors and has minimal activity or affinity for other neurotransmitter receptors and other potential targets such as calcium channels.
  - In clinical studies, the mean decrease in urge incontinence episodes was 50 % and the mean decrease in urinary frequency was 17 %.
- Trospium (Sanctura):
  - Trospium is a quaternary ammonium compound that elicits antispasmodic and antimuscarinic effects.
  - It antagonizes acetylcholine effect on muscarinic receptors.
  - Parasympathetic effect reduces smooth muscle tone in the bladder.
  - Trospium is indicated to treat symptoms of overactive bladder (e.g., urinary incontinence, urgency, frequency).
- Fesoterodine (Toviaz):
  - Fesoterodine is a competitive muscarinic receptor antagonist.
  - The antagonistic effect results in decreased bladder smooth muscle contractions.
  - It is indicated for symptoms of overactive bladder (e.g., urinary urge incontinence, urgency, and frequency).

11.10 Botulinum Toxin Type A

- It binds to the presynaptic nerve endings of cholinergic neurons, resulting in a marked reduction in bladder contractions.
- Botulinum A toxin injections into the detrusor muscle have been shown to be a potentially valuable approach in the neurogenic overactive bladder.
- It is also associated with reduced requirement for oral medication and improved quality of life.
- Urodynamic efficacy lasts for about 6 months, after which repeated injections are necessary.
- Repeated botulinum A toxin injections could be considered to postpone or avoid surgical procedures in the small minority of children not responding to standard therapy with CIC and anticholinergics.
- However, further investigations are required, given remaining concerns about costs and long-term efficacy and safety of prolonged botulinum A toxin administration.

11.11 Tricyclic Antidepressant Drugs

- These drugs are used to treat major depression; however, they have an additional use that is treatment of bladder dysfunction.
- They function to increase norepinephrine and serotonin levels.

- In addition, they exhibit anticholinergic and direct muscle relaxant effects on the urinary bladder.
- Imipramine hydrochloride (Tofranil)
  - Imipramine hydrochloride is a typical tricyclic antidepressant.
  - It facilitates urine storage by decreasing bladder contractility and increasing outlet resistance.
  - It has alpha-adrenergic effect on the bladder neck and antispasmodic effect on detrusor muscle.
  - Imipramine hydrochloride has a local anesthetic effect on bladder mucosa.
- Amitriptyline hydrochloride (Elavil)
  - Amitriptyline hydrochloride is a tricyclic antidepressant with sedative properties.
  - It increases circulating levels of norepinephrine and serotonin by blocking their reuptake at nerve endings and is ineffective for use in urge incontinence.
  - However, it is extremely effective in decreasing symptoms of urinary frequency in women with pelvic floor muscle dysfunction.
  - Amitriptyline hydrochloride restores serotonin levels and helps break the cycle of pelvic floor muscle spasms.
- Infection:
  - In the absence of reflux, patients with UTIs are treated symptomatically.
  - Patients with vesicoureteral reflux are often placed on prophylactic antibiotics to reduce the chance of upper UTI or pyelonephritis.
  - Bacteriuria is seen in as many as 55 % of patients who have received clean intermittent catheterization (CIC).
  - Patients who are completely asymptomatic do not need treatment.
- Vesicoureteral Reflux (VUR):
  - VUR occurs in 3–5 % of infants with myelodysplasia and is usually associated with detrusor hyperreflexia or DSD.
  - Treatment consists of:
    - Antibiotic prophylaxis to prevent infection
    - Anticholinergic medications to lower detrusor filling and voiding pressures
    - A method of bladder emptying, most commonly CIC
  - In children with lower-grade reflux who empty their bladders completely, treatment may be limited to prophylactic antibiotics.
  - In children with high-grade reflux, CIC is started to ensure complete emptying.
  - Children unable to empty their bladders, regardless of reflux, are treated with CIC.
  - Children with detrusor hyperreflexia (with or without hydronephrosis) are started on anticholinergic therapy to decrease intravesical pressures and possibly decompress the upper urinary tracts.
    - Reflux treated in this manner has shown a dramatic response, resolving in 30–55 % of children.
    - Avoid the Crede maneuver (voiding by suprapubic pressure) in children with reflux because it can increase pressures and aggravate the degree of reflux.
- Inability to empty bladder:
  - Because most patients with myelodysplasia are unable to spontaneously empty their bladders, numerous methods have been devised to potentiate bladder emptying.
  - CIC on a regular basis is a safe, effective method of emptying the bladder and, if performed under clean conditions, does not appear to significantly increase the risk of infection.
  - The practice of CIC has changed the treatment of and approach to patients with neurogenic bladders.
  - Currently, urinary diversion is rarely performed in pediatric patients.
- Incontinence:
  - Medical therapy consists of anticholinergic medications to increase the functional bladder volume and to reduce involuntary contractions.
  - Additionally, alpha agonists have been used infrequently in children to increase sphincter tone.
- Impaired bowel function:
  - Often, children with myelodysplasia have disturbances of bowel as well as urinary function.
  - This is managed most commonly with mild laxatives, such as mineral oil, combined

    with enemas or digital stimulation to facilitate removal of bowel contents.
  - Constipation can affect bladder emptying adversely
  - The need for a program to combat constipation by maintaining soft stools and facilitating complete evacuation of bowel contents is an integral part of treatment in children with myelodysplasia.
- Consider all patients with myelodysplasia of spina bifida to have a latex allergy and make every effort to avoid exposure to latex from birth. Gloves, catheters, crib pads, and bottle nipples are all potential sources and may exacerbate hypersensitivity.

11.12 Surgical Management

- Surgery for neurogenic bladder, although once performed on most patients, is now primarily reserved for patients:
  - Who have progressive renal damage despite maximal medical therapy
  - With extremely noncompliant bladders
  - Who wish to improve their continence
- Most procedures are designed to allow adequate low-pressure bladder storage (thereby protecting the upper urinary tract), to correct persistent reflux and prevent renal scarring, or to aid with continence.
- Procedures to correct vesicoureteral reflux:
  - Ureteral reimplantation
    - Ureteral reimplantation can be performed in patients with recurrent symptomatic UTIs despite adequate bladder drainage and antibiotic prophylaxis or in patients with persistent high-grade reflux with demonstrated renal scarring.
    - The purpose of the procedure is to create a nonrefluxing connection between the ureter and the bladder.
    - This treatment is very effective, provided that a regimen is implemented to ensure a low-pressure reservoir and bladder emptying.
  - Dextranomer/hyaluronic acid (Deflux) injection
    - This is a much less invasive way to address vesicoureteral reflux.
    - Deflux (a viscous gel consisting of dextranomer microspheres and hyaluronic acid) is injected cystoscopically just beneath the ureteral orifice to prevent reflux.
    - It is performed as an outpatient procedure with excellent success rates (70–85 % with a single injection) and can be repeated if necessary.
  - Vesicostomy
    - In infants who cannot be catheterized or who demonstrate worsening renal function despite medical therapy and CIC, cutaneous vesicostomy can be performed to establish adequate bladder drainage.
    - Vesicostomy is an effective temporary procedure that may be reversed at any time.
- Bladder augmentation:
  - Bladder augmentation is an option in patients with small bladder capacity and poor bladder compliance despite maximal medical therapy.
  - The bladder capacity is increased by anastomosing a detubularized segment of bowel to the bladder. As a result of this, the storage pressures can be lowered, minimizing upper urinary tract deterioration and improving continence.
  - This can be associated with complications including metabolic derangements, mucous production, stone formation, and hematuria.
  - If incontinence is a significant problem, a bladder neck sling procedure can be performed along with bladder augmentation.
- Urinary diversion:
  - Formal urinary diversion for neurogenic bladder is very rarely performed today.
  - The risks of major abdominal surgery, metabolic derangements, and long-term upper

urinary tract deterioration are present with urinary diversion.
  - Since the advent of CIC, some patients who underwent incontinent urinary diversion as infants have undergone successful undiversion with bladder augmentation.
- Procedures for incontinence:
  - As patients get older, continence becomes an issue in their lives.
  - Several procedures have been developed to improve continence, with the hope to promote more-independent living.
  - Dextranomer/hyaluronic acid (Deflux) bladder neck injection
    - This procedure consists of cystoscopically injecting dextranomer/hyaluronic acid into the bladder neck to increase outlet resistance.
    - It has been shown to improve continence, but complete cures are unpredictable and the durability of the procedure is still being evaluated.
  - Bladder neck sling
    - This procedure entails placing a sling of either autologous tissue or synthetic polypropylene mesh beneath the urethra in order to increase outlet resistance.
    - There are several variations to the procedure, but overall success rates range from 60 % to greater than 85 %, with a number of patients becoming fully continent.
  - Detrusor myoplasty
    - Though uncommon, this procedure has the possibility of increasing bladder contractility in some patients.
    - It is performed by harvesting the patient's latissimus dorsi muscle and microsurgically transplanting it so that it wraps around the bladder.
    - This has allowed some patients to spontaneously void and reduce their dependence on catheterization.
  - Stem cell injection
    - This is still purely experimental, but preliminary studies have shown some promise.
    - In this procedure, stem cells are cystoscopically injected into the urinary sphincter.
    - The goal of therapy is to increase sphincter activity and improve continence.

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Urinary Tract Infection in Infants and Children

12

12.1 Introduction

- Urinary tract infection (UTI) is one of the most common infections in infants and children.
- The occurrences of symptomatic UTI for the first time in boys and girls is highest during the first year of life and decreases markedly after that.
- The workup of infants who present with fever should include evaluation for urinary tract infection.
- Urinary tract infection (UTI) in infants and children is divided into two categories:
  - Upper urinary tract infection (Pyelonephritis)
  - Lower urinary tract infection (Cystitis)
- Most episodes of UTI during the first year of life are pyelonephritis.
- It is not uncommon for infants younger than 3 months to present with fever without a localizing source and these patients should be evaluated for UTI.
- After age 2 years, UTI in the form of cystitis is common among girls.
- Rarely, UTI maybe the first presentation of an important underlying structural or neurogenic abnormality of the urinary tract.
- The most common causative organisms are bowel flora, typically gram-negative rods.
  - *Escherichia coli* is the most common organism.
  - The most common pathogen is Escherichia coli, accounting for approximately 85 % of urinary tract infections in children.
  - Klebsiella, Proteus, Enterobacter, Citrobacter, Staphylococcus saprophyticus, and Enterococcus.
  - Other organisms that can cause urinary tract infection include fungi (*Candida* species) and viruses.
- The incidence of UTIs varies based on age, sex, and gender.
- The exact incidence of UTIs is not known but in the United States UTIs are estimated to affect 2.4–2.8 % of children.
- The overall prevalence of UTI in infants presenting with fever was 7.0 %.
- Approximately 7 % of children 2–24 months of age presenting with fever without a source were diagnosed with a UTI.
- 8 % of children 2–19 years of age presenting with possible urinary symptoms were diagnosed with a UTI.
- The frequency of UTIs is also variable according to age and sex. The rates of UTIs in girls according to age as follows:
  - 0–3 months (7.5 %)
  - 3–6 months (5.7 %)
  - 6–12 months (8.3 %)
  - >12 months (2.1 %)
- In boys, the incidence of UTIs is also influenced by whether the child is circumcised or not.

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A.H. Al-Salem, *An Illustrated Guide to Pediatric Urology*, DOI 10.1007/978-3-319-44182-5_12

  - The rate in uncircumcised febrile boys <3 months of age was 20.7 %
  - The rate in circumcised febrile boys <3 months of age was 2.4 %
  - The rate in uncircumcised febrile boys 6–12 months of age was 7.3 %
  - The rate in circumcised febrile boys 6–12 months of age was 0.3 %
  - However, contamination is very common in obtaining a urine sample from a male when the foreskin cannot be retracted and the rates in uncircumcised males are, undoubtedly, overestimates.
- During the first few months of life, the incidence of UTI in boys exceeds that in girls.
- By the end of the first year and thereafter, first-time and recurrent UTIs are most common in girls.
- The incidence of UTI in children aged 1–2 years is 8.1 % in girls and 1.9 % in boys.
- In a study of infants presenting to pediatric emergency departments, the prevalence of UTI in infants younger than 60 days with a temperature greater than 100.4 °F (38 °C) was 9 %.
- Guidelines from the American Academy of Pediatrics recommend considering the diagnosis of UTI in patients aged 2 months to 2 years who present with unexplained fever.
- Acute urinary tract infections are relatively common in children, with 8 % of girls and 2 % of boys having at least one episode of UTIs by 7 years of age.
- Renal parenchymal defects are present in 3–15 % of children within 1–2 years of their first diagnosed urinary tract infection.
- Clinical signs and symptoms of a urinary tract infection depend on the age of the child, but all febrile children 2–24 months of age with no obvious cause of infection should be evaluated for urinary tract infection.
- Prophylactic antibiotics do not reduce the risk of subsequent urinary tract infections, even in children with mild to moderate vesicoureteral reflux.
- Constipation should be avoided to help prevent urinary tract infections.
- The reference standard for the diagnosis of UTI is a single organism cultured from a specimen obtained at the following concentrations:
  - Suprapubic aspiration urine specimen, greater than 1,000 colony-forming units per mL
  - Catheter urine specimen, greater than 10,000 colony-forming units per mL
  - Clean-catch, midstream urine specimen, 100,000 colony-forming units per mL or greater.
- Urological abnormalities known to be associated with URIs:
  - Baseline abnormalities of the urogenital tract have been reported in up to 3.2 % of healthy, screened infants.
  - Obstructive anomalies are found in up to 4 %
  - Vesicoureteral reflux in 8–40 % of children being evaluated for their first UTI.
  - Children younger than 2 years may be at greater risk of parenchymal defects than older children.

12.2 Etiology

- Bacterial infections are the most common cause of UTI in infants and children.
- *E coli* is the most frequent organism causing UTI responsible for 75–90 % of UTIs.
- Other bacterial organisms that cause UTI include:
  - *Klebsiella* species
  - *Proteus* species
  - *Enterococcus* species
  - *Staphylococcus saprophyticus*
  - *Streptococcus* group B, especially among neonates
  - *Pseudomonas aeruginosa*
- Other relatively rare organisms responsible for UTIs include Fungi (*Candida* species) and viruses (Adenovirus)
- Adenovirus is a rare cause of hemorrhagic cystitis.
- Genes that are possibly responsible for increased susceptibility to recurrent UTIs

include *HSPA1B*, *CXCR1*, *CXCR2*, *TLR2*, *TLR4*, and *TGFβ1*.

- Susceptibility to UTI may be increased by any of the following factors:
  - Alteration of the periurethral flora by antibiotic therapy
  - Anatomic anomalies of the renal system leading to urinary stasis
  - Bowel and bladder dysfunction
  - Constipation
- The use of antibiotics for other infections increases the risk for UTIs.
- The use of antibiotics alter the gastrointestinal and periurethral flora, disturbing the urinary tract's natural defense against colonization by pathogenic bacteria.
- Neurogenic or anatomic abnormalities of the urinary bladder may also cause voiding dysfunction.
- Anatomic abnormalities of the renal system are known to predispose to UTIs.
- Constipation, with the rectum chronically dilated by feces, is an important cause of voiding dysfunction and UTIs.
- For male infants, neonatal circumcision substantially decreases the risk of UTI.
  - The Risk is particularly high during the first 3 months of life.
  - It was shown that during the first year of life, the rate of UTI was 2.15 % in uncircumcised boys, versus 0.22 % in circumcised boys.
  - In another study, it was shown that in febrile boys younger than 3 months, UTI was present in 2.4 % of circumcised boys and in 20.1 % of uncircumcised boys.

12.3 Pathophysiology

- UTIs result when colonized organisms in the periurethral area ascend into the bladder via the urethra to cause cystitis.
- From the bladder, organisms can spread up the urinary tract to the kidneys and cause pyelonephritis.
- Sometimes, the organisms can spread to the bloodstream and cause bacteremia or septicemia.
- Normally, urine in the proximal urethra and urinary bladder is sterile.
- Access of microorganisms to the urethra and urinary bladder can result from several factors including:
  - Stasis and turbulent urine flow during normal voiding
  - Voiding dysfunction
  - Urethral catheterization
  - Colonization of organisms during episodes of sepsis
  - Direct spread from the perineum
- The short female urethra and its proximity to fecal flora may, in part, explain the predominance of UTI in girls after the neonatal period.
- Mortality related to UTI is exceedingly rare in otherwise healthy children.
- Cystitis may cause voiding symptoms but it is not associated with long-term kidney damage.
- Approximately 10–30 % of children with UTI develop some renal scarring.
- Long-term complications of pyelonephritis are:
  - Renal parenchymal scarring
  - Hypertension
  - Impaired renal function
  - End-stage renal disease

12.4 Clinical Features

- A urinary tract infection (UTI), is divided into two types depending on the level of infection.
- Acute cystitis or bladder infection, is an infection that affects the lower urinary tract.
- Acute pyelonephritis (infection of the kidney), is an infection that affects the upper urinary tract.
- All febrile children between 2 and 24 months of age with no obvious cause of infection should be evaluated for UTI, with the exception of circumcised boys older than 12 months.
- Older children who present with fever should be evaluated for UTI if the clinical presentation points toward a urinary source.
- The clinical features of patients with UTIs are variable and differ according to the patient's age.

- Neonates and infants up to age 2 months who have pyelonephritis usually do not have symptoms localized to the urinary tract and UTI is discovered as part of an evaluation for neonatal sepsis.
- Boys are at increased risk of UTI if younger than 6 months, or if younger than 12 months and uncircumcised.
- Girls are generally at an increased risk of UTI, particularly if younger than 1 year.
- Infants from 2 to 36 months of age with a fever of >39 °C and no other source for fever on history or physical examination could have a UTI, and should have urine collected for urinalysis. Unless this test is completely normal, they should then have urine collected by catheter or suprapubic aspirate and sent for culture.
- When UTI is suspected in toilet-trained children, a midstream urine sample rather than a catheter or suprapubic aspiration specimen should be submitted for urinalysis and culture.
- Children with possible UTI who require antibiotic treatment immediately for other indications, such as suspected bacteremia, should have urine collected for urinalysis, microscopy and culture. The test sample should be midstream urine if the child is toilet trained, and a catheter or suprapubic aspiration or clean-catch specimen if not, and obtained before starting antibiotics.
- Over diagnosis of UTI is a common problem, leading to overuse of antibiotics and unnecessary imaging.
- Urines collected by bag should never be used for diagnosis of UTI. Urines with low colony counts, mixed growth or no pyuria are usually contaminated.
- Children <2 years of age should be investigated after their first febrile UTI with a renal and bladder ultrasound to identify significant renal abnormalities and grade IV or V VUR.
- A voiding cystourethrogram (VCUG) is not indicated with a first febrile UTI when the renal and bladder ultrasound is normal.
- VCUG may detect vesicoureteric reflux (VUR). Low-grade VUR (grade 1–2) usually resolves without permanent damage, but high-grade (grade 4–5) VUR may require surgical correction.
- Physical examination findings can be nonspecific but may include suprapubic tenderness or costovertebral angle tenderness.
- Neonates with UTI may present with the following symptoms:
  - Jaundice
  - Fever
  - Failure to thrive
  - Poor feeding
  - Vomiting
  - Irritability
- Infants and children aged 2 months to 2 years lack symptoms localized to the urinary tract but may present with the following symptoms:
  - Poor feeding
  - Fever
  - Loss of appetite, poor oral intake and vomiting
  - Strong and foul smelling urine
  - Abdominal pain or suprapubic pain
  - Irritability
  - Voiding symptoms suggestive of cystitis, with crying on urination
- Children aged 2–6 years may present with the following symptoms:
  - Vomiting
  - Abdominal, flank, back pain or suprapubic pain
  - Loss of appetite
  - Irritability
  - Fever
  - Strong and foul smelling urine
  - Enuresis
  - Dysuria, urgency, frequency
- Children older than 6 years may present with the following symptoms:
  - Fever
  - Vomiting
  - Abdominal pain
  - Flank/back pain
  - Strong and foul smelling urine
  - Dysuria, urgency, frequency
  - Enuresis
  - Incontinence

- Older children with pyelonephritis often have tenderness of the flank or costovertebral angle.
- Those with cystitis may have suprapubic tenderness with or without a palpable bladder.
- The finding of hypertension should raise suspicion of hydronephrosis or renal parenchyma disease.

12.5 Investigations and Diagnosis

- Complete blood count (CBC)
- Blood cultures (in patients with suspected bacteremia or urosepsis)
- Serum creatinine and blood urea nitrogen
- Serum electrolyte levels
- The diagnosis of a urinary tract infection in children depends on a positive urinary culture.
- Contamination poses a frequent challenge depending on the method of urine collection used.
- A blood culture in febrile infants and older patients who are clinically ill, toxic, or severely febrile.
- Urine analysis:
  - Urinalysis alone is not sufficient for diagnosing UTI.
  - However, urinalysis can help in identifying febrile children who should receive antibacterial treatment while culture results from a properly collected urine specimen are pending.
  - Rapid urine tests (also known as dipsticks or macroscopic urinalysis) remain useful for the diagnosis of UTI.
  - Urine dipstick test:
    - Urine dipstick testing alone may provide an adequate initial UTI screen.
    - Urine dipstick tests for UTI include leukocyte esterase, nitrite, blood, and protein.
    - Positive dipstick readings for nitrite, leukocyte esterase, or blood may suggest a UTI.
    - Dipstick tests have sensitivities of approximately 85–94 %.
    - Dipstick tests for blood and protein have poor sensitivity and specificity in the detection of UTI and may be misleading.
    - Automated microscopy has better specificity and likelihood ratios than dipstick testing, but it had slightly lower sensitivity.
  - The nitrite test:
    - This measures the conversion of dietary nitrate to nitrite by Gram-negative bacteria.
    - A positive nitrite test makes UTI very likely.
    - The test may be falsely negative if the bladder is emptied frequently or if an organism that does not metabolize nitrate (including all Gram-positive organisms) is the cause of infection.
    - The test for nitrite is more specific but less sensitive.
  - The leukocyte esterase test:
    - This is an indirect measure of pyuria and, therefore, may be falsely negative when leukocytes are present in low concentration.
    - Leukocyte esterase is the most sensitive single test in children with a suspected UTI.
    - A negative leukocyte esterase result greatly reduces the likelihood of UTI, whereas a positive nitrite result makes it much more likely; the converse is not true, however.
  - A microscopic urinalysis:
    - This is useful to determine whether there are white blood cells in the urine, which is a sensitive indicator of inflammation associated with infection.
    - Microscopic examination of spun urine can evaluate for the presence of white blood cells (WBCs), red blood cells (RBCs), bacteria, casts, and skin contamination (e.g., epithelial cells).
    - Approximately 10–20 % of pediatric patients with UTIs have normal urinalysis results.

    - Pyuria is 73 % sensitive and 81 % specific for the diagnosis of UTI.
    - However, the definition of pyuria is not uniform in the literature.
    - The finding of ten white blood cells per microliter in uncentrifuged urine specimen is reported to be a more sensitive indicator of UTI.
    - Or, the finding of >5 white blood cells per high-power field in uncentrifuged urine specimen is a more sensitive indicator of UTI.
    - The presence of pyuria of at least ten white blood cells per high-power field and bacteriuria are recommended as the criteria for diagnosing UTI with microscopy.
    - The absence of pyuria does not exclude a UTI, especially in infants <2 months of age.
    - The question is whether infants with positive urine cultures but no pyuria have contamination or asymptomatic bacteruria rather than a UTI.
    - Bacteria and yeast seen on microscopic urinalysis are often contaminants.
    - The combination of pyuria and bacteruria on urinalysis should raise suspicion for a UTI.
    - On a suprapubic aspirate, the presence of five or more WBCs per high-power field or the presence of ten or more WBC/μL suggests an infection. Gram stain of unspun urine may reveal organisms.
    - A hemacytometer measures cells per volume and has been found to be more sensitive and specific than standard microscopic examination.
    - The combination of hemacytometer cell count and Gram stain has been shown in studies to have a sensitivity approaching 95 %.
  - A child with a negative urine dipstick for nitrites and leukocyte esterase and no pyuria or bacteruria on microscopic examination has a <1 % chance of having a UTI.
- Urine culture and sensitivity:
  - Urine collection must be done before starting antibiotics because a single dose of an effective antibiotic rapidly sterilizes the urine.
  - Microscopy and urine culture should be performed in children younger than 3 years instead of dipstick testing.
  - The American Academy of Pediatrics (AAP) criteria for the diagnosis of UTI in children 2–24 months are the presence of pyuria and/or bacteriuria on urinalysis and of at least 50,000 colony-forming units (CFU) per mL of a uropathogen from the quantitative culture of a properly collected urine specimen.
  - In neonates younger than 2 months of age, the criteria for the diagnosis of UTI include the presence of lower amounts of a single pathogen (10,000–50,000 CFU/mL)
  - The use of “urine bags” to collect samples is discouraged due to the high rate of contamination when cultured, and catheterization is preferred in those not toilet trained.
  - Urine sample for culture:
    - A midstream, clean-catch specimen may be obtained from children who have urinary control.
    - Suprapubic aspiration or urethral catheterization should be used in infants or children unable to void on request.
    - Suprapubic aspiration is the method of choice for obtaining urine from the following patients:
      - Uncircumcised boys with a redundant or tight foreskin
      - Girls with tight labial adhesions,
      - Children of either sex with clinically significant periurethral irritation
  - The diagnosis of UTIs in infants and children is based on colony-forming units (CFU) per mL of an uropathogen depending on the method used to collect the urine sample.
    - 10^5 CFU/mL is used for a “clean-catch” mid-stream urine sample
    - 10^4 CFU/mL is used for catheter-obtained urine specimens

    - 10^2 CFU/mL is used for suprapubic urine aspirations
  - In young children, urine samples collected with a bag are unreliable compared with samples collected with a catheter. Therefore, in a child who is unable to provide a clean-catch specimen, catheterization should be considered. If urine cannot be cultured within 4 h of collection, the sample should be refrigerated.
  - Culture of a urine specimen from a sterile bag attached to the perineal area has a false-positive rate so high that this method of urine collection is not suitable for diagnosing UTI. However, a culture of a urine specimen from a sterile bag that shows no growth is strong evidence that UTI is absent.
  - Multiple organisms may be present in patients with structural abnormalities.
- In previously well children who have not been on antibiotics, UTIs are usually due to:
  - *Escherichia coli*
  - *Klebsiella pneumoniae*
  - *Enterobacter* species
  - *Citrobacter* species
  - *Serratia* species
  - In adolescent females only, *Staphylococcus saprophyticus*
- Mixed growth or growth of other organisms usually indicates that the urine is contaminated.
- When children are started on antibiotics for possible UTI, the diagnosis must be reassessed once the results of all investigations are available and antibiotics stopped if UTI appears to be unlikely.
- The American Academy of Pediatrics recommends renal ultrasound and voiding cystourethrogram in all children less than 2 years old who have had a urinary tract infection.
- The National Institute for Health and Care Excellence only recommends routine imaging in those less than 6 months old or who have unusual findings.
- Imaging studies:
  - In general imaging studies are not indicated for infants and children with a first episode of cystitis or for those with a first febrile UTI.
  - Imaging should only be performed when it is likely to alter management.
  - The choice of imaging should be guided by the safety, cost and accuracy of the procedure to be done.
  - Current common imaging options for children with UTI include renal/bladder ultrasound (RBUS), radiographic (e.g., VCUG) and radioisotope (e.g., dimercaptosuccinic acid [DMSA]) techniques.
- Ultrasonography of the urinary tract:
  - Ultrasonography is the imaging study of choice in children with UTI.
  - Urinary ultrasonography is safe, cheap, noninvasive study, radiation free and easy to perform.
  - The AAP Clinical Practice Guidelines recommend routine ultrasonography of the urinary tract after a first febrile UTI in children aged 2–24 months.
  - Other indications for ultrasonography of the urinary tract after a febrile UTI in pediatric patients are as follows:
    - Delayed or unsatisfactory response to treatment of a first febrile UTI
    - An abdominal mass or abnormal voiding (dribbling of urine)
    - Recurrence of febrile UTI after a satisfactory response to treatment
    - Finally, renal ultrasonography should be considered for any child with a first febrile UTI in whom good follow-up cannot be ensured.
- Voiding Cystourethrography (VCUG):
  - Traditionally, VCUG has been recommended for infants and children after a first febrile UTI.
  - This is based on assumptions that most upper UTIs occur because of urinary bladder infection and that vesicoureteral reflux (VUR) transfers bacteria in the bladder to the kidney.
  - The AAP no longer recommends the routine use of VCUG after the first UTI.
  - There is some concern, however, that without VCUG after the first documented

febrile UTI, some cases of significant reflux disease will be missed.
- VCUG is recommended after a second episode of febrile UTI.
- VCUG is indicated if renal and bladder ultrasonography reveals:
  - Hydronephrosis
  - Renal scarring
  - Obstructive uropathy
  - Masses or if complex medical conditions are associated with the UTI.
  - Other findings suggestive of high-grade VUR
- VCUG should also be performed if a patient has a recurrence of a febrile UTI, even if previous ultrasonographic examination findings were unremarkable.
- Children who respond to treatment for a UTI but afterwards demonstrate an abnormal voiding pattern may need to undergo an evaluation for voiding dysfunction. This evaluation may include standard VCUG.
- In the past, a voiding cystourethrogram (VCUG) was recommended routinely for children between 2 months and 2 years of age who had a febrile UTI, but this is no longer recommended practice.
- A VCUG is the optimal method for diagnosing VUR and for assessing the degree of VUR and the anatomy of the male urethra.
- There are several drawbacks to performing a VCUG including expense, exposure to radiation, and the risk of causing a UTI and discomfort for the child.
- A recent change in practice is that antibiotic prophylaxis is no longer recommended for children with grade I through III VUR because the number needed to receive prophylaxis for 1 year to prevent one UTI is small. Therefore, routine imaging of infants with VCUG after the first UTI is no longer suggested unless abdominal ultrasound is suggestive of renal abnormalities or obstruction, or high-grade VUR. A child with normal kidney structure is not at significant risk of developing chronic kidney disease because of UTIs.
- A VCUG is usually indicated for children <2 years of age with a second well-documented UTI.

- Where available, a nuclear cystogram (NCG) may be used in place of a VCUG to assess for VUR using radioisotopes.
  - NCG delivers less radiation than a VCUG but is less readily available and provides poor anatomical detail for the male urethra.
  - NCG can miss posterior urethral valves.
  - NCG can be used in place of VCUG as the initial test for VUR investigation in females and in follow-up studies for both sexes.
- A DMSA scan:
  - This can be used to diagnose acute pyelonephritis (when performed during acute illness) and to identify renal scars (when performed months following the acute illness).
  - DMSA scan is associated with radiation exposure and is not likely to alter management; thus, a DMSA is primarily useful when the diagnosis of acute UTI or of repeated UTIs is in doubt.

12.6 Management

- According to AAP guidelines for the treatment of initial UTIs in febrile infants and children aged 2–24 months old, antibiotics can be given orally or parenterally, with the choice of route based on practical considerations.
- Oral antibiotics should not be used in a child who is acutely ill or toxic, has persistent vomiting, or has moderate to severe dehydration. Daily follow-up and good compliance are essential with this approach.
- The AAP recommends basing the choice of antibiotic on local sensitivity patterns if known.
- The choice can be adjusted, if necessary, when results of sensitivity testing become available.
- Antibiotics can be given for 7 or 14 days.
- Amoxicillin has traditionally been a first-line antibiotic for UTI, but increased rates of E.

coli resistance have made it a less acceptable choice.

- Studies have found higher cure rates with trimethoprim/sulfamethoxazole (Bactrim, Septra).
- Other choices include amoxicillin/clavulanate (Augmentin) or cephalosporins, such as cefixime (Suprax), cefpodoxime, cefprozil (Cefzil), or cephalexin (Keflex).
- Patients with a nontoxic appearance may be treated with oral fluids and antibiotics. Toxic-appearing patients must be aggressively treated with intravenous (IV) fluids and parenteral antibiotics.
- Most cases of uncomplicated UTI respond readily to outpatient antibiotic treatments without further sequelae.
- Antibiotic resistance among uropathogens is increasing dramatically, however.
- Previous antibiotic exposure (i.e., for otitis media) has been found to be associated with drug-resistant UTIs and should be kept in mind when choosing empiric therapy.
- Children with acute pyelonephritis can be treated effectively with either oral antibiotics or with 2–4 days of IV therapy followed by oral therapy. Oral therapy with a third-generation cephalosporin was as effective as traditional inpatient parenteral treatment.

Antibiotics used for oral treatment of a urinary tract infection

Antibiotic	Dose
Sulfamethoxazole and trimethoprim (SMZ-TMP) (Bactrim, Septra)	30–60 mg/kg SMZ, 6–12 mg/kg TMP divided q12 h
	(8–10 mg/kg divided q12 h)
Amoxicillin	50 mg/kg/day (divided in three doses)
Amoxicillin and clavulanic acid (Augmentin)	*20–40 mg/kg divided q8 h
	*25–45 mg/kg divided q12 h
Cephalexin (Keflex)	*50–100 mg/kg divided q6 h
	*25–50 mg/ kg divided q6–12 h
Ciprofloxacin	30 mg/g/day (divided in two doses)
Cefpodoxime	10 mg/kg divided q12 h
Cefixime (Suprax)	8 mg/kg q24 h or divided q12 h
Nitrofurantoin	5–7 mg/kg divided q6 h
Cefprozil (Cefzil)	30 mg/kg divided q12 h

- A Cochrane review of children up to 18 years of age with pyelonephritis found no difference between oral antibiotics (10–14 days) and IV antibiotics (3 days) followed by oral antibiotics (10 days) with respect to duration of fever or subsequent renal damage.
- Similarly, no significant differences were found comparing IV antibiotics (3–4 days) followed by oral antibiotics, versus IV antibiotics alone for 7–14 days.
- Most experts recommend initial treatment with oral antibiotics for febrile UTIs in nontoxic children with no known structural urological abnormality, assuming that they are likely to receive and tolerate every dose.
- Data on oral therapy is limited for infants 2–3 months of age, so close follow-up is warranted for this age group. Some experts recommend initial IV antibiotics for this age group.
- While waiting for antibiotic susceptibility results for the likely bacterial pathogen, clinicians should make an empirical choice of antibiotics based on local susceptibility patterns. Aminoglycoside levels and renal function need to be monitored when the aminoglycoside is continued for >48 h.
- If clinical findings indicate that immediate antibiotic therapy is indicated, a urine specimen for urinalysis and culture should be obtained before treatment is started.
- Common choices for empiric oral treatment are:
  - A second- or third-generation cephalosporin

  - Amoxicillin/clavulanate, or sulfamethoxazole-trimethoprim (SMZ-TMP).
- Patients with a nontoxic appearance may be treated with oral fluids and antibiotics.
- Hospitalization is necessary for the following patients with UTI:
  - Patients who are toxemic or septic
  - Patients with signs of urinary obstruction or significant underlying disease
  - Patients who are unable to tolerate adequate oral fluids or medications
  - Infants younger than 2 months with febrile UTI (presumed pyelonephritis)
  - All infants younger than 1 month with suspected UTI, even if not febrile
- Antibiotics suggested for parenteral treatment are as follows:
  - Ceftriaxone
  - Cefotaxime
  - Ampicillin
  - Gentamicin
- Infants and children with febrile UTI should be treated with antibiotics for 7–10 days.
- Oral antibiotics can be administered as initial treatment when the child has no other indication for admission to hospital and is considered likely to receive and tolerate every dose.
- There is no evidence that children with UTIs and documented bacteremia who have a rapid clinical response to antibiotics require intravenous antibiotics or a longer course of antibiotics.
- The choice of antibiotics should be guided by the resistance pattern of common urinary pathogens in the community and changed to a less broad spectrum agent, if practical, when the sensitivity of the pathogen is known.
- Consider circumcision of male neonates to prevent UTIs.
- A systematic review concluded that routine circumcision in boys does not reduce the risk of UTI enough to justify the risk of surgical complications.
- The AAP policy statement on circumcision is that “the health benefits of newborn male circumcision outweigh the risks and that the procedure’s benefits justify access to this procedure for families who choose it.” The AAP notes that the benefits of the procedure include prevention of UTIs.
- Children with acute pyelonephritis can be treated effectively with oral antibiotics (e.g., amoxicillin/clavulanate, cefixime, ceftibuten [Cedax]) for 10–14 days or with short-courses (2–4 days) of intravenous therapy followed by oral therapy for a total of 10–14 days.
- Follow-up assessment to confirm an appropriate clinical response should be performed 48–72 h after initiating antimicrobial therapy in all children with UTI.
- Culture and susceptibility results may indicate that a change of antibiotic is necessary.
- If expected clinical improvement does not occur, consider further evaluation.
- Infants <8 weeks old:
  - The diagnosis in infants <8 weeks old with a febrile UTI is usually based on fever and on positive results from a urine specimen obtained by catheterization.
  - In this age 10,000 colonies/mm^3 defines bacteriuria.
  - Infants with such findings are usually hospitalized and receive parenteral antibiotic therapy.
  - However, clinical judgment may indicate that home treatment is appropriate.
  - Parenteral antibiotics may be used with daily follow-up until the patient is afebrile for 24 h.
  - Complete 10–14 days of therapy with an oral antibiotic that is active against the infecting bacteria.
- Children with cystitis:
  - Children with cystitis usually do not require special medical care other than appropriate antibiotic therapy and symptomatic treatment if voiding symptoms are marked.
  - Antibiotic therapy is started on the basis of clinical history and urinalysis results before the diagnosis is documented.
  - A 4-day course of an oral antibiotic agent is recommended for the treatment of cystitis.
  - Nitrofurantoin can be given for 7 days or for 3 days after obtaining sterile urine.

  - A 2- to 4-day course of oral antibiotics appears to be as effective as a 7- to 14-day course in children with lower UTIs.
  - Guidelines from the American Academy of Pediatrics recommend limiting fluoroquinolone therapy to patients with UTIs caused by Pseudomonas aeruginosa or other multidrug-resistant, gram-negative bacteria. Ciprofloxacin (Cipro) is used for complicated UTIs and pyelonephritis attributable to E. coli in patients 1–17 years of age.
  - If the clinical response is not satisfactory after 2–3 days, alter therapy on the basis of antibiotic susceptibility
  - Symptomatic relief for dysuria consists of increasing fluid intake (to enhance urine dilution and output), acetaminophen, and nonsteroidal anti-inflammatory drugs (NSAIDs)
  - If voiding symptoms are severe and persistent, add phenazopyridine hydrochloride (Pyridium) for a maximum of 48 h
- Children with Complicated Pyelonephritis:
- Pyelonephritis is considered complicated when it occurs in:
  - A neonate or an infant
  - A patient with an anatomic abnormality of the urinary tract or abnormal renal function
  - A patient who is immunocompromised
    - Start IV fluids, usually at 1–1.5 times the usual maintenance rate.
    - Parenteral treatment with a third-generation cephalosporin (e.g., ceftriaxone, cefotaxime) is appropriate initial empiric coverage for a complicated UTI and pyelonephritis to cover for ampicillin-resistant, gram-negative pathogens.
    - Add ampicillin if gram-positive cocci are present in the urinary sediment or if no organisms are observed.
    - Gentamicin is an alternative empiric choice and may be considered in patients with cephalosporin allergy.
    - Monitor renal function and blood aminoglycoside levels if gentamycin is required for more than 48 h.
    - The results of urine culture and sensitivity studies are usually available within 48 h.
      - If the pathogen is sensitive to the antibiotic used and the child is improving, continue treatment via the parenteral route until the child has been afebrile for 24–36 h, has improved clinically, and is able to retain oral medications.
      - An oral antibiotic that is effective against the infecting organism may then be substituted for parenteral therapy.
      - The hospitalized patient who is responding to treatment can go home after 48–72 h.
      - Continue oral antibiotics for a total of 10–14 days.
- Antibiotic prophylaxis is no longer recommended for grades I through III VUR or pending results of the renal and urinary bladder ultrasound.
- Antibiotic prophylaxis is more often recommended for children with high-grade reflux (grade 3–5).
- The current AAP guidelines do not recommend prophylactic antibiotics to prevent UTI recurrences.

Antibiotics used for parenteral treatment of a urinary tract infection

Drug	Dose and route
Ceftriaxone	50–75 mg/kg/day IV/IM as a single dose or divided q12 h
Cefotaxime	150 mg/kg/day IV/IM divided q6–8 h
Ampicillin	100 mg/kg/day IV/IM divided q8 h
Gentamicin	*Term neonates <7 days: 3.5–5 mg/kg/dose IV q24 h
	*Infants and children <5 years: 2.5 mg/kg/dose IV q8 h or single daily dosing with normal renal function of 5–7.5 mg/kg/dose IV q24 h
	*Children ≥5 year: 2–2.5 mg/kg/dose IV q8 h or single daily dosing with normal renal function of 5–7.5 mg/kg/dose IV q24 h
Ampicillin	200 mg/kg IV/day (divided every 6 h)
Tobramycin	5–7.5 mg/kg once per day

- Children with grade IV or V VUR or a significantly abnormal renal and urinary bladder ultrasound should be evaluated further for a possible surgical management.
- Constipation should be addressed in infants and children who have had a UTI to help prevent subsequent infections.
- There is some evidence that cranberry juice decreases symptomatic UTIs over 12-months, particularly in women with recurrent UTIs.
- The effectiveness of cranberry juice in children is less certain, and the high dropout rate in studies indicates that cranberry juice may not be acceptable for long-term prevention.

Antibiotics used for prophylaxis

Antibiotic	Single daily dose
Sulfamethoxazole and trimethoprim (SMZ-TMP)	5–10 mg/kg SMZ, 1–2 mg/kg TMP PO
Trimethoprim	1–2 mg/kg PO
Nitrofurantoin	1–2 mg/kg PO
Cephalexin	10 mg/kg PO

Further Reading

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Bladder Exstrophy-Epispadias Complex

13

13.1 Introduction

- Bladder exstrophy (also known as Ectopia vesicae) is a congenital anomaly that exists as part of the exstrophy-epispadias complex.
- It is characterized by protrusion of the open urinary bladder through a defect in the lower abdominal wall.
- Bladder exstrophy-epispadias complex is a spectrum of rare congenital malformations involving the urinary, genital, and musculoskeletal systems in which the bladder remains open through a lower abdominal defect.
- Bladder exstrophy-epispadias-cloacal exstrophy complex is the most severe and comprises a spectrum of anomalies involving the urinary tract, genital tract, musculoskeletal system and sometimes the intestinal tract.
- The bladder exstrophy-epispadias complex comprises a spectrum of congenital abnormalities that includes (Figs. 13.1 and 13.2):
  - Classic bladder exstrophy
  - Epispadias
  - Cloacal exstrophy
  - Other rare variants
  - The spectrum often include abnormalities of the bony pelvis, pelvic floor, and genitalia
- The underlying embryologic mechanism leading to this spectrum of anomalies is unknown but it is believed that all represent a spectrum of the same embryological defect. It is thought to result from failed reinforcement of the cloacal membrane by underlying mesoderm.

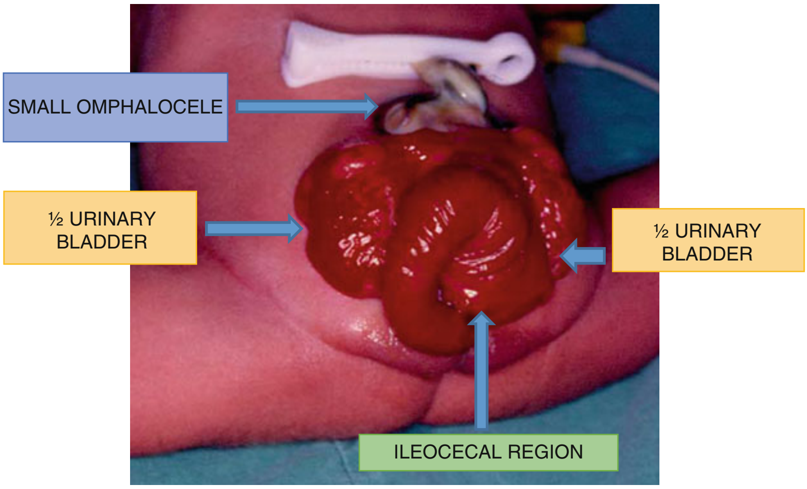

Fig. 13.1 A clinical photograph showing classic cloacal exstrophy. Note the open urinary bladder into two halves and the ileocecal region protruding in the middle of the bladder. Note the small omphalocele

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A.H. Al-Salem, *An Illustrated Guide to Pediatric Urology*, DOI 10.1007/978-3-319-44182-5_13

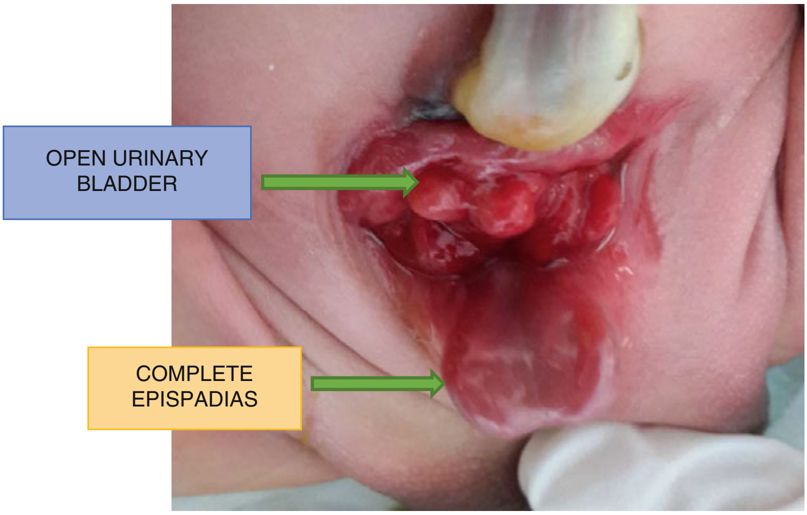
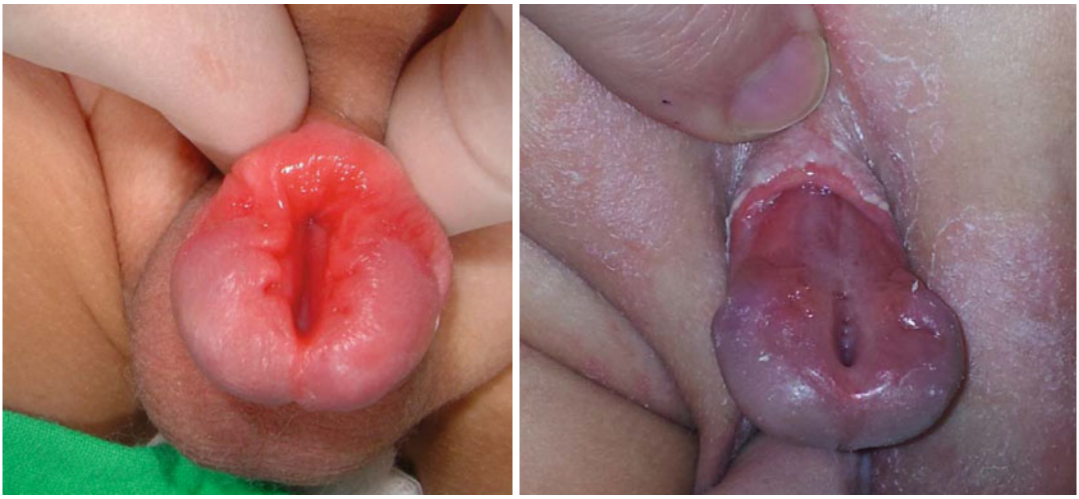


Fig. 13.2 A clinical photograph showing classic bladder exstrophy. Note the open urinary bladder. Note also the associated complete epispadias

- The incidence:
  - The birth prevalence of classic bladder exstrophy has been estimated to be between 1 in 10,000 and 1 in 50,000 livebirths. Others reported a prevalence of 3.3 per 100,000 births.
  - Males are affected two to three times more often than females.
  - Isolated epispadias occurs in approximately 1 in 112,000 live male births and 1 in 400,000 live female births.
  - The prevalence of Cloacal exstrophy is 1 in 200,000–400,000 births.
- The risk of bladder exstrophy in children born to parents with bladder extrophy is approximately 500-fold greater than the general population.
- The classic manifestation of bladder exstrophy is characterized by:
  - A defect in the abdominal wall occupied by both the exstrophied bladder as well as a portion of the urethra
  - A flattened puborectal sling
  - Separation of the pubic symphysis
  - Shortening of the pubic ramii
  - External rotation of the pelvis
  - Females also have:
    - A displaced and narrowed vaginal orifice
    - A bifid clitoris
    - Divergent labia
- Patients diagnosed intra-uterine with bladder extrophy should be referred to specialized centers for further evaluation and management.
- Modern therapy is aimed at surgical reconstruction of the bladder and genitalia.
  - Staged Repair of bladder Exstrophy:
    - The initial step is closure of the abdominal wall, often requiring a pelvic osteotomy.
    - This leaves the patient with penile epispadias and urinary incontinence.
    - At approximately 6 months of age the patient then undergoes repair of the epispadias after testosterone stimulation.
    - Finally, bladder neck repair usually is done around the age of 4–5 years, though this is dependent upon a bladder with adequate capacity and, most importantly, an indication that the child is interested in becoming continent.
  - Complete Primary Repair of bladder Exstrophy:
    - The bladder closure is combined with an epispadias repair.
- Epispadias is a congenital malformation of males in which the urethra opens on the upper surface (dorsum) of the penis.
- Epispadias is an uncommon congenital malformation of the penis and rarely occur as an isolated defect.



Figs. 13.3 and 13.4 Clinical photographs showing epispadias. In the first picture, the epispadias is limited to the glans while in the second one there is complete epispadias

- It is seen more commonly as part of the epispadias-exstrophy complex.
- It is now possible to diagnose exstrophy-epispadias complex antenatally using ultrasound and recently fetal magnetic resonance imaging. This is important to council the parents and also to transfer these patients in-utero to specialized centers with a team experienced in their management. The antenatal ultrasonography findings suggestive of exstrophy-epispadias complex include the following:
  - Failure to visualize the bladder
  - Lower abdominal wall mass
  - Low-set umbilical cord
  - Abnormal genitalia
  - Increased pelvic diameter
  - Omphalocele
  - Limb abnormalities
  - Myelomeningocele
  - Elephant Trunk sign from prolapsed intestine
- Early attempts at bladder exstrophy repair were unsuccessful and for many years the management for exstrophy consisted of excision of the exstrophic bladder and urinary diversion commonly by ureterosigmoidostomy.
- Anatomical defects in classic bladder exstrophy:
  - The urinary bladder is open on the lower abdomen
  - The urinary bladder mucosa is fully exposed through a triangular fascial defect on the lower abdomen.
  - The abdominal wall appears long because of a low-set umbilicus on the upper edge of the urinary bladder plate.
  - The distance between the umbilicus and anus is foreshortened.
  - The rectus muscles diverge distally, attaching to the widely separated pubic bones.
  - Inguinal hernias are frequently associated with bladder extrophy.
    - >80 % of males, and >10 % of females with bladder extrophy have inguinal hernias.
    - This is due to wide inguinal rings and the lack of an oblique inguinal canal.
  - The phallus (Figs. 13.3, 13.4, and 13.5):
    - It is short and broad.
    - It is characterized by an upward curvature (dorsal chordee).
    - The glans lies open and flat like a spade.
    - The dorsal component of the foreskin is absent.
    - The urethral plate is open and extends the length of the phallus.
    - The bladder plate and urethral plate are in continuity, with the verumontanum

and ejaculatory ducts visible within the prostatic urethral plate.
  - The anus is anteriorly displaced with a normal sphincter mechanism.
- Anatomical defects in epispadias:
  - The urethra opens on the upper surface (dorsum) of the penis. The extent of this is variable from only the glanular part to the whole urethra.
  - The pubic symphysis is generally widened but only mildly.
  - The rectus muscles are divergent distally
  - This can be an isolated anomaly or more commonly part of the extrophy-epispadias complex.
- Anatomical defects in cloacal exstrophy (Fig. 13.6):
  - The bladder is open and separated into two halves
  - The exposed interior of the cecum is within it.
  - Openings to the remainder of the hindgut and to one or two appendices are evident within the cecal plate.
  - The terminal ileum may prolapse as a "trunk" of bowel onto the cecal plate.
  - The phallus:
    - The penis is generally quite small and bifid
    - A hemiglans is located just caudal to each hemibladder.
    - Infrequently, the phallus may be intact in the midline.
    - In females, the clitoris is bifid and two vaginas are present.
  - The anus is absent.
  - Nearly all patients have an associated omphalocele.

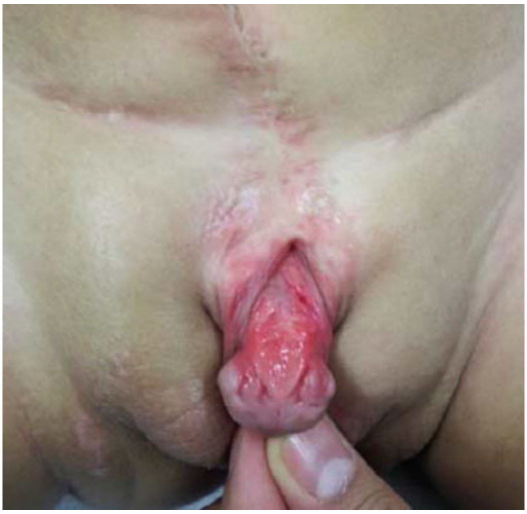


Fig. 13.5 A clinical photograph showing epispadias as part of classic extrophy. Note the site of closure of bladder extrophy

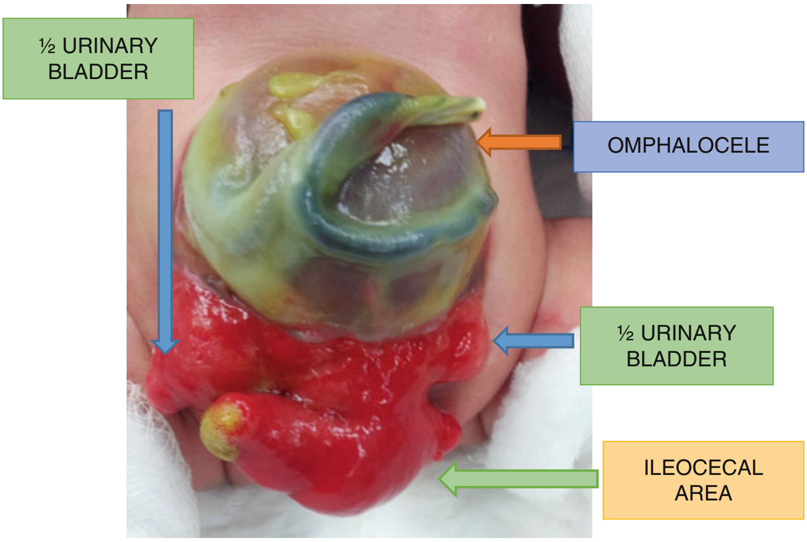


Fig. 13.6 A clinical photograph showing cloacal extrophy. Note the urinary bladder divided into two halves. Note the ileocecal junction in the middle between the two halves of the bladder. Note also the associated large omphalocele

  - Musculoskeletal defects
    - The pubic symphysis is widely separated.
    - The rectus muscles diverge distally but remain attached to the pubis.
    - External rotation of the innominate bones results in a waddling gait but does not appear to result in orthopedic problems later in life.
  - Neurologic defects
    - In cloacal exstrophy, as many as 95 % of patients have myelodysplasia.
    - This may include myelomeningocele, lipomeningocele, meningocele, or other forms of occult dysraphism.
    - These patients are at risk of neurologic deterioration, and they should be observed closely.
- Anatomical defects in exstrophy variants:
  - The pubic symphysis is widely separated
  - The rectus muscles diverge distally.
  - The umbilicus is low in position or elongated.
  - A small superior bladder opening or a patch of isolated bladder mucosa may be present.
  - The intact bladder may be externally covered by only a thin membrane.
  - Isolated ectopic bowel segments have been reported.
  - Genitalia generally are intact, though epispadias can occur.

13.2 Embryology

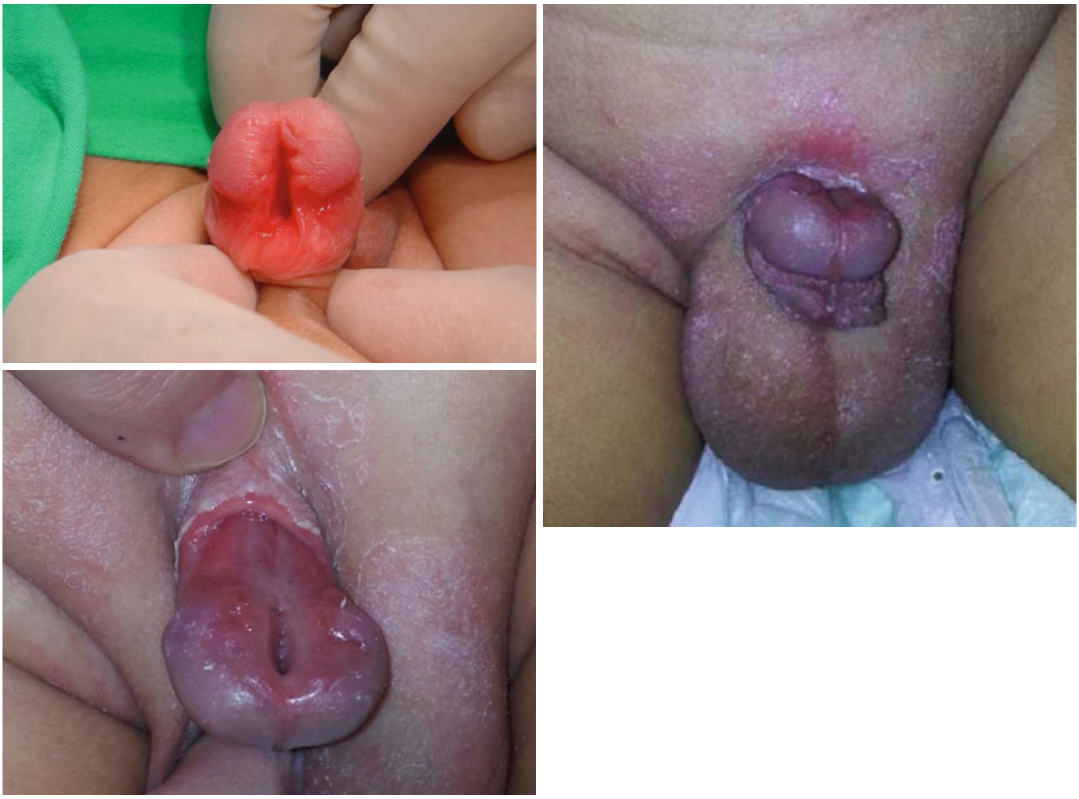
- The exact cause of these anomalies is not known but it is believed that all represent a spectrum of the same embryological defect.
- Embryoogically, the primitive cloaca is divided by the urorectal septum into the anterior urogenital sinus and posteriorly the hindgut.
- This occurs during the first trimester at approximately the same time as maturation of the anterior abdominal wall.
- Mesodermal ingrowth between the ectodermal and endodermal layers of the bilaminar cloacal membrane results in formation of the lower abdominal musculature and pelvic bones.
- After mesenchymal ingrowth occurs, downward growth of the rectal septum divides the cloaca into a bladder anteriorly and a rectum posteriorly.
- The genital tubercles migrate medially and fuse in the midline cephalad to the dorsal membrane before it perforates.
- Failure of mesenchyme to migrate between the ectodermal and endodermal layers of the lower abdominal wall leads to deficient lower abdominal wall and instability of the cloacal membrane.
- The cloacal membrane is subject to premature rupture depending on the extent of the infraumbilical defect.
- Premature rupture of the cloacal membrane before its caudal translocation leads to this spectrum of anomalies.
- The timing and location of rupture of the cloacal membrane dictate the patient's presentation along the exstrophy-epispadias spectrum.
- The stage of development when the membrane rupture occurs determines whether bladder exstrophy, cloacal exstrophy, or epispadias results.
- Epispadias occurs if the rupture produces a division or nonunion at the distal end of the urinary tract.
- The timing of the rupture of this cloacal defect determines the severity of the disorder.
  - Classic bladder exstrophy (60 %)
  - Exstrophy variants (30 %)
  - Cloacal exstrophy (10 %)
- Rupture of the cloacal membrane after complete separation of the genitourinary anteriorly and the gastrointestinal tract posteriorly results in classic bladder exstrophy.
- Rupture of the cloacal membrane prior to descent of the urorectal septum and separation of the genitourinary and the gastrointestinal tract leads to cloacal exstrophy.
- Cloacal exstrophy must be distinguished from persistent cloaca or cloacal malformation.
- This is the most extreme form of anorectal malformation in female infants in which there

is incomplete separation of the urinary tract, genital tract and hindgut.
- The exact embryological defect is not known and several theories have been proposed to explain this.
- Marshall and Muecke theory is based on an abnormal lower overdevelopment of the cloacal membrane, which prevents the medial migration of the mesenchymal tissue which impairs the proper development of the abdominal wall.
- Ambrose and O'Brian postulated that an abnormal development of the genital hillocks with fusion in the midline below rather than above the cloacal membrane result in the exstrophy defect.
- Another hypothesis describes an abnormal caudal insertion of the body stalk with failure of the interposition of the mesenchymal tissue in the midline. As a consequence of this failure, translocation of the cloaca into the depths of the abdominal cavity does not occur. A cloacal membrane that remains in a superficial infraumbilical position represents an unstable embryonic state with a strong tendency to disintegrate.

13.3 Epispadias

13.3.1 Introduction

- Epispadias, bladder extrophy and cloacal extrophy are major embryological defects that are known to be associated with long term morbidity. With the recent advances in surgical techniques including bladder closure, pelvic osteotomies, and traction and immobilization the majority of these patients can achieve full continence, adequate sexual function, and improvement in quality of life.
- In males, the external urethral opening (external meatus) is normally located at the tip of the penis.
- In females, the external urethral opening is normally located between the clitoris and the vagina.
- Epispadias is the least severe form of Bladder Exstrophy-Epispadias Complex and it is characterized by a dorsally open urethral meatus with mild pubic diastasis and a closed anterior abdominal wall and bladder.
- Epispadias is a very rare congenital malformation of the male or female urethra, in which the urethra opens dorsally.
- In females with epispadias, there is a fissure in the upper wall of the urethra and out of the body through an opening above the clitoris or it can present as a double clitoris.
- In males with epispadias, the urethra opens on the superior surface of the penis. The extent of this opening is variable. It can involve only the glans or extend to involve the whole shaft of penis.
- This differentiates it from hypospadias which is a congenital defect, in which the urethra opens on the ventral surface of the penis.
- Epispadias is very rare, with an estimated incidence of approximately 1 in 100,000 live male births.
- It is extremely rare in females.
- Complete epispadias is a rare congenital malformation.
  - It occurs in 1 in every 117,000 male births
  - It occurs in only 1 of every 484,000 female births
- Epispadias rarely occur as an isolated defect.
- It is commonly seen as part of the exstrophy-epispadias complex.
- Diastasis of the pubic bone and external displacement of the hips is seen in severe cases of epispadias.
- In males, epispadias is characterized by (Figs. 13.7, 13.8, 13.9, and 13.10):
  - The urethra opens on the dorsum of the penis. This can affect only the glans or extend to affect the whole urethra.
  - The normal urethra is replaced by a broad mucosal strip lying on the dorsum of the corpora cavernosa.
  - A short phallus.
  - A penis that is typically broad.
  - Dorsal chordee (marked upward curvature of the penis).
- Patients with isolated epispadias have a low incidence of associated abnormalities but those with the more severe form of exstrophy-epispadias complex are at a slightly increased risk for associated malformations



Figs. 13.7, 13.8, and 13.9 Clinical photographs showing epispadias. The first is a glanular type of epispadias while the lower two show complete epispadias involving the whole urethra. Note the urethral opening on the dorsum of the penis

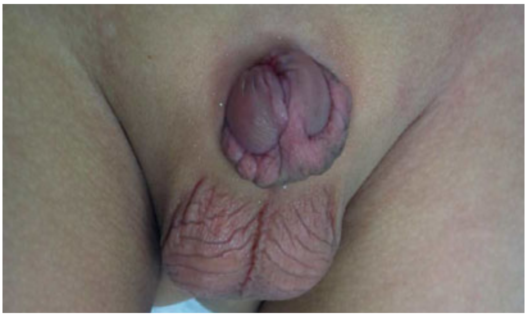


Fig. 13.10 A clinical photograph showing epispadias. Note the short phallus which is also broad. Note also the upward chordee of the penis and the urethral opening on the dorsum of the penis

- These include:
  - Hydroureters
  - Hydronephrosis
  - Vesicoureteral reflux.
  - These patients are also at increased risk for retrograde ejaculation when they reach adolescence because of failure of bladder neck to close completely.

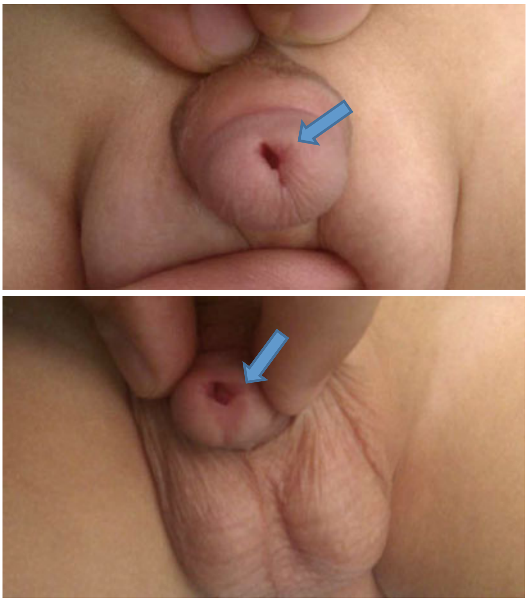
13.3.2 Etiology

- The penis is formed by the corpus spongiosum surrounding the urethra and by two corpora cavernosa.
- These are composed of erectile tissue surrounded by the tunica albuginea (Buck fascia) and the dartos fascia more superficially.
- Normally, the male urethra runs through the penile shaft, ventrally to the corpora cavernosa, and meets with the meatus at the tip of the glans.
- The exact etiology of eispadias is not known.

- Epispadias and exstrophy of the bladder are considered varying degrees of the same disorder.
- Epispadias results from defective migration of the paired primordia of the genital tubercle.
- These fuse on the midline to form the genital tubercle at the fifth week of embryologic development.

13.3.3 Classification

- The extent of epispadias is variable.
- It can present as a small dimple on the tip of the glans penis just above the normal urethral opening (Figs. 13.11 and 13.12).
- If the urethra and bladder are involved, the epispadias is severe and this is part of the spectrum of malformations called the exstrophy-epispadias complex (Fig. 13.13).
- Commonly, the classification of epispadias is based on the location of the urethral meatus as follows:
  - Glandular epispadias (Figs. 13.11, 13.12, and 13.14):
    - The extent of epispadias is limited to the glans of the penis.
    - This is the rarest type.
  - Penile epispadias (Figs. 13.15 and 13.16):
    - The epispadias opening extends along the whole shaft of the penis.
  - Penopubic epispadias (complete):
    - The epispadias opening extends to the pubic bone.
  - Part of the exstrophy-epispadias complex (Figs. 13.17 and 13.18).
- Patients with glanular and about one-third of those penile epispadias usually have good



Figs. 13.11 and 13.12 Clinical photographs showing glandular epispadias. Note the urethral opening on the dorsum of the penis. It appear as a dimple on the dorsum of the glans

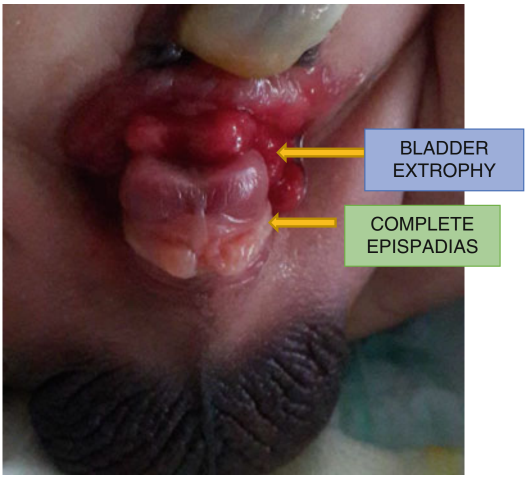


Fig. 13.13 A clinical photograph showing complete epispadias as part of the extrophy-epispadias complex. Note the dorsal chordee

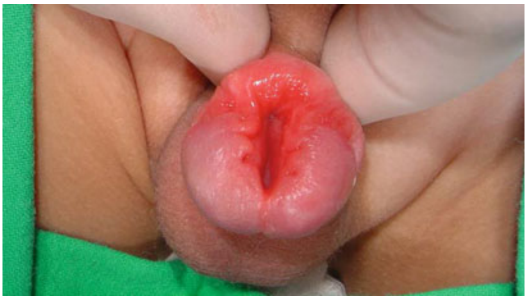
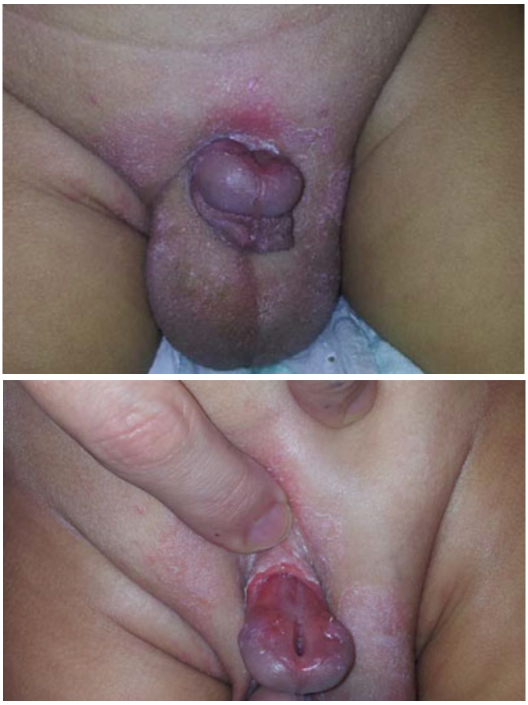


Fig. 13.14 A clinical photograph showing glandular epispadias. Note the urethra opening on the dorsum of the penis and limited to the glans of the penis

prognosis with normal urinary capacity and no urine incontinence.

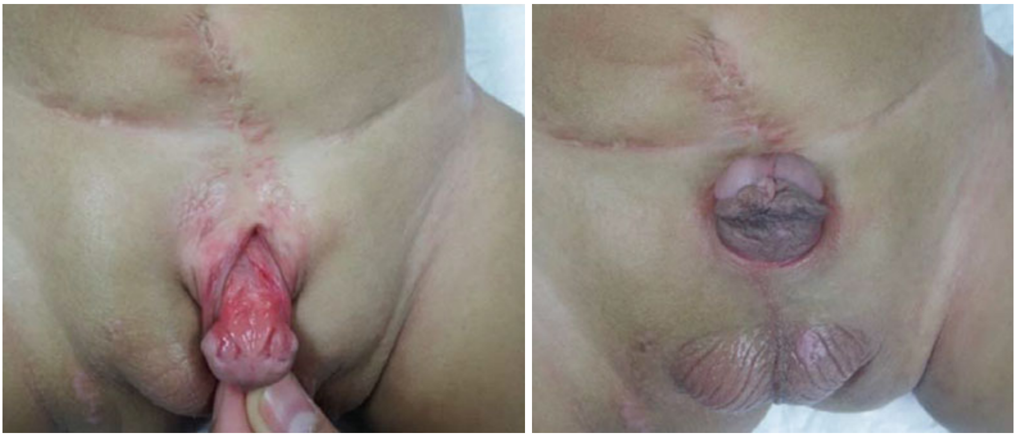
- In most cases of penopubic epispadias, and approximately two-thirds of those with penile epispadias have urine incontinence.
- These patients and those with exstrophy-epispadias complex will require reconstructive bladder neck surgery to achieve urine continence.
- Currently, about 80 % of patients with male epispadias patients are continent postoperatively.
- The remaining patients who are still incontinent may require later bladder neck reconstruction.
- It is also estimated that about 87–100 % of isolated female epispadias are continent postoperatively.



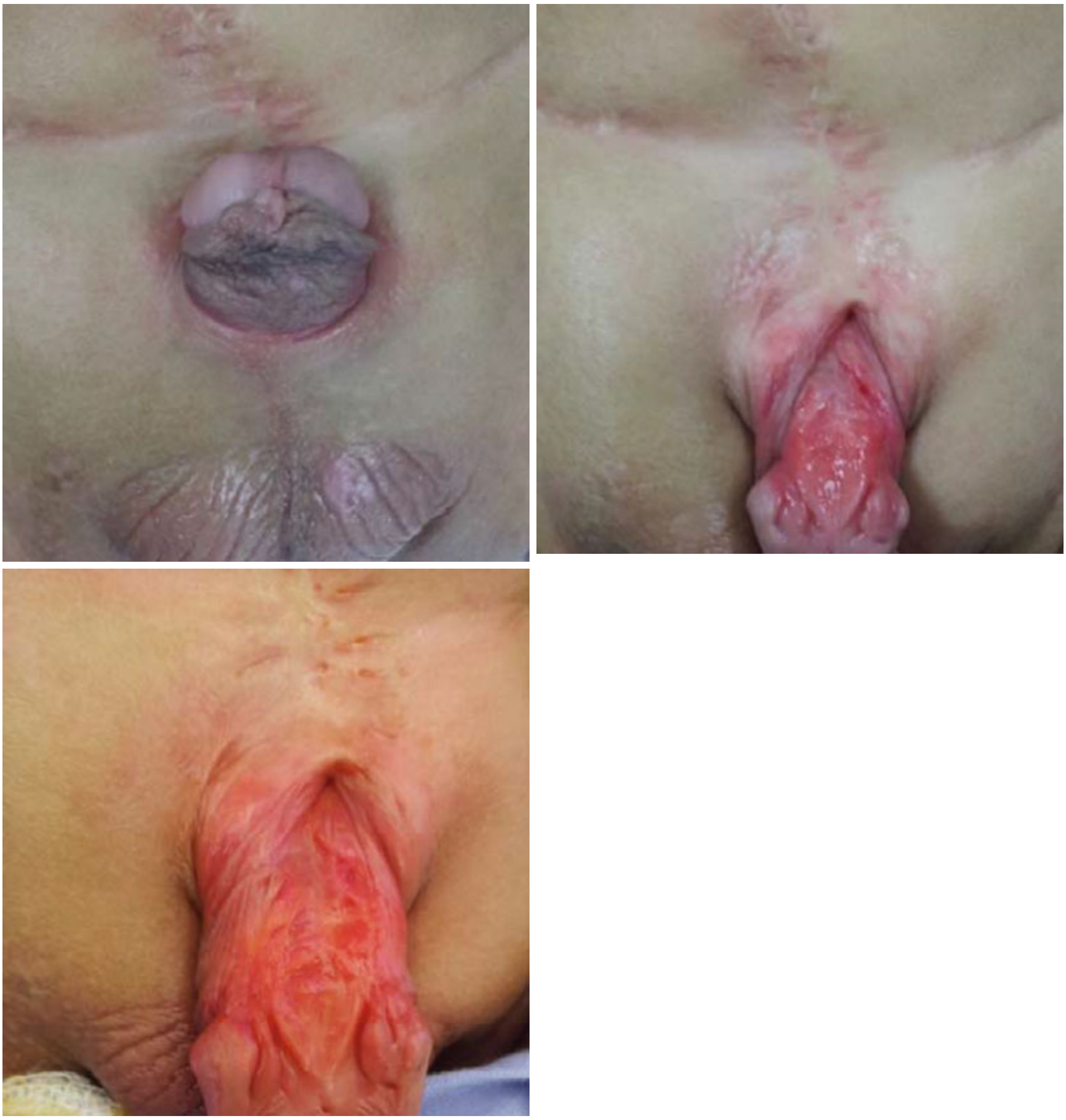
Figs. 13.15 and 13.16 Clinical photographs showing penile epispadias. Note the dorsal chordee and the urethral opening on the dorsum of the penis and extending along the shaft of the penis

13.3.4 Treatment

- The goals of treatment of epispadias are:
  - To lengthen and straighten the penis by correcting dorsal bend and chordee.
  - To create a functionally and cosmetically acceptable penis with an external urethral meatus at the tip of the penis.
  - To establish urinary continence and preserve fertility in those with the more severe forms.
- Patients with epispadias are born with a very small or severely underdeveloped penis. These patients are usually treated with long acting testosterone preoperatively to enlarge the size of the penis (Figs. 13.19, 13.20, and 13.21).



Figs. 13.17 and 13.18 Clinical photographs showing epispadias as part of the bladder extrophy. Note the scars after closure of the urinary bladder



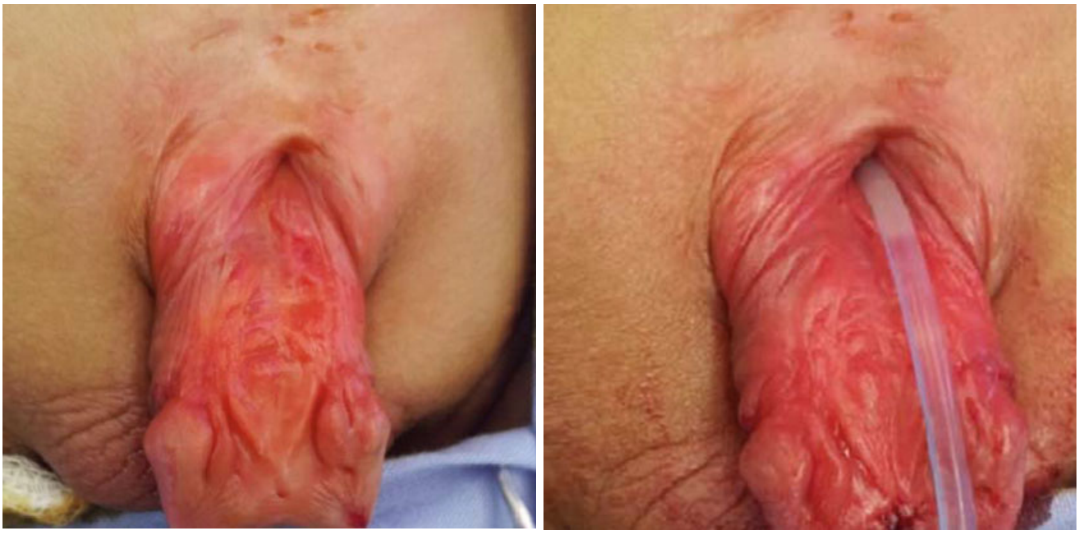
Figs. 13.19, 13.20, and 13.21 Clinical photographs showing epispadias before testosterone, after testosterone and at the time of surgery. Note the increase in the size of the penis following testosterone injections

- They are given one or a maximum of three doses at 3–4 weeks intervals (2 mg/kg/dose). Others use topical testosterone.
- The surgical treatment of epispadias differs according to the complexity of the malformation.
- A staged approach has often been used for the management of the exstrophy-epispadias complex.
- Currently, epispadias are treated with single stage procedures.
- There are three surgical techniques used to correct epispadias:
  - – The Cantwell-Ransley procedure.
  - – The Young procedure.
  - – The complete disassembly procedure.
    - In this technique the two corpora cavernosa and a single corpus spongiosum are totally separated and the three components are reassembled and the urethra constructed in such a way that the urethra is in its normal position.

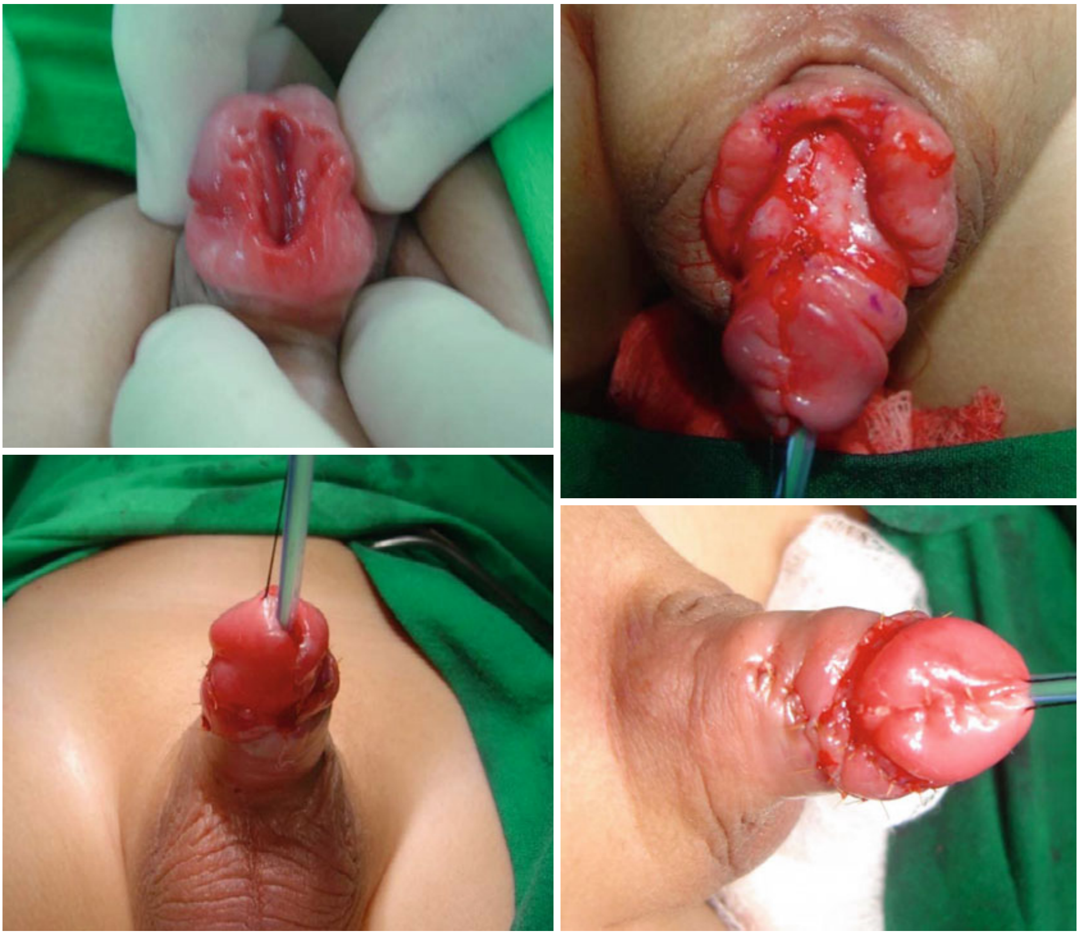
  - A large number of children with the exstrophy-epispadias complex will subsequently require bladder neck repair to achieve continence.

13.3.5 Surgical Repair of Male Epispadias (Figs. 13.22, 13.23, 13.24, 13.25, 13.26, 13.27, 13.28, 13.29, 13.30, 13.31, 13.32, 13.33, 13.34, 13.35, and 13.36)

- Intramuscular or topical testosterone is given preoperatively to increase the size of the penis.
- The surgical repair of epispadias include:
  - Correction of dorsal chordee:
    - This is achieved by mobilizing the urethral plate from the underlying corpora from the level of glans down to the prostatic urethra.
    - The corporal bodies are anastomosed at the dorsal medial aspect over the tubularized urethra.
    - Persistent chordee is corrected by cavernostomy.
  - Glanular and urethral reconstruction:
    - The urethral meatus is correctly positioned using a reversed meatal advancement and glanuloplasty technique.
  - Closure of penile skin
- The modern modified Cantwell-Ransley repair is the most commonly used technique to repair epispadias.
- Mitchell and Bagli have described a further modification of Cantwell-Ransley repair "complete penile disassembly technique".
  - The urethral plate and each corporeal body along with its hemiglans are dissected completely free from each other.
  - The urethra is then tubularized and placed into an anatomic, ventral position.
  - This method of epispadias repair is often performed at the time of primary bladder closure, the combination of which is called "complete primary repair of bladder exstrophy".
  - This technique may be complicated by ischemia as a result damage to the blood supply during dissection.
  - The lateral dissection during this procedure can result in neurovascular bundle injury and consequent erectile dysfunction.



Figs. 13.22 and 13.23 Clinical photographs showing epispadias being repaired. This was part of the exstrophy-epispadias complex that was treated in two stages. Note the broad penis. The length of the penis increased as a result of testosterone injections

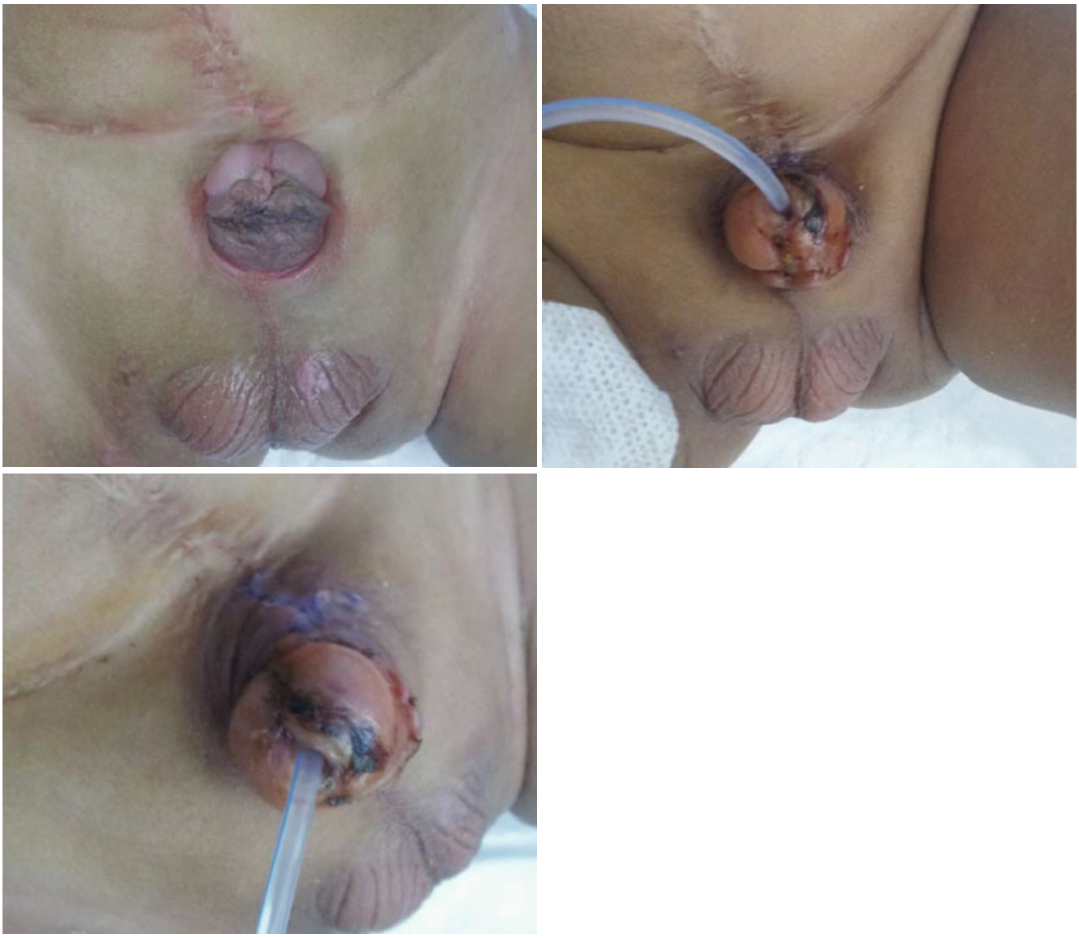


Figs. 13.24, 13.25, 13.26, and 13.27 Clinical operative photographs showing repair of glandular epispadias. Note the good size and normal shape of the penis

  - The tubularized urethra is usually shorter than the actual corpora, resulting in hypospadias which necessitate further urethroplasty.
- Postoperatively, the patients undergo yearly gravity cystograms to measure bladder capacity. Bladder augmentation may be necessary for those with small bladder capacity.
- Procedures to improve continence are usually done at 5–9 years of age.
  - The Young-Dees-Leadbetter bladder neck reconstruction.
  - Bladder neck transection, bladder augmentation, and continent urinary diversion can be done simultaneously in those with small bladder capacity.

13.3.6 Female Epispadias

- Female epispadias is extremely rare.
- The reported incidence is approximately 1 of 500,000–600,000 live girls.
- Epispadias in females is commonly associated with separated pubic bones.
- Female epispadias is characterized by:
  - A bifid clitoris.
  - Diastases of the corpora cavernosa.
  - Flattening of the mons.
  - Separation of the labia.
- The diagnosis of epispadias in females is always delayed as the defect may not be obvious.
- The bladder neck is almost always involved in these patients leading to urinary incontinence.



Figs. 13.28, 13.29, and 13.30 Clinical operative photographs showing repair of epispadias after closure of bladder extrohy. Note the scar of closure of the bladder extrophy and the normal size and shape of the penis

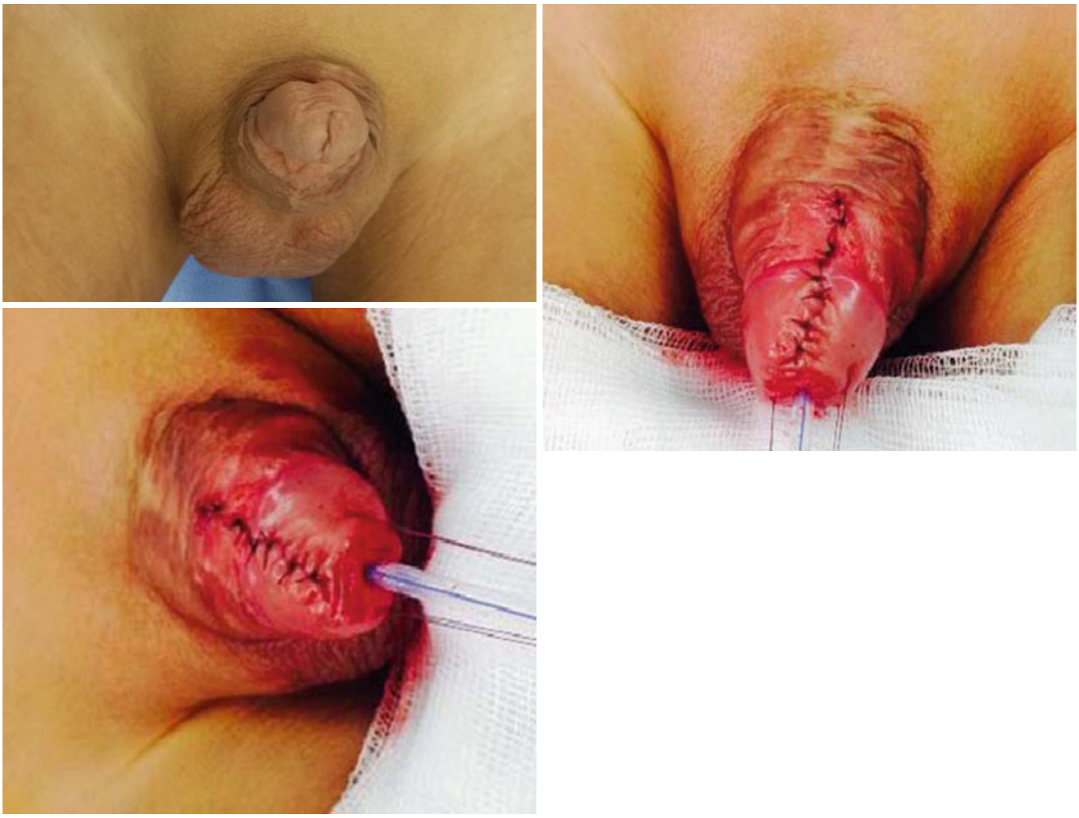
- Repair of female epispadias is much simpler than male epispadias.
- The two parts of the clitoris are sutured together and the urethra is positioned in its normal place.
- The prognosis of these patients is good and fertility is not affected.

13.3.7 Surgical Repair of Female Epispadias

- Repair of isolated female epispadias is generally done along with Young-Dees-Leadbetter bladder neck reconstruction, monsplasty, and clitoroplasty.
- Like male epispadias patients, if the bladder template does not grow after bladder neck reconstruction, the patient may require bladder neck transection, bladder augmentation, and continent urinary diversion.
- Bilateral iliac osteotomies may be necessary to correct the associated pubic diastasis.

13.3.8 Prognosis

- The prognosis for male patients with epispadias depends on the extent of the defect.
- Most patients with mild degrees of epispadias do well.



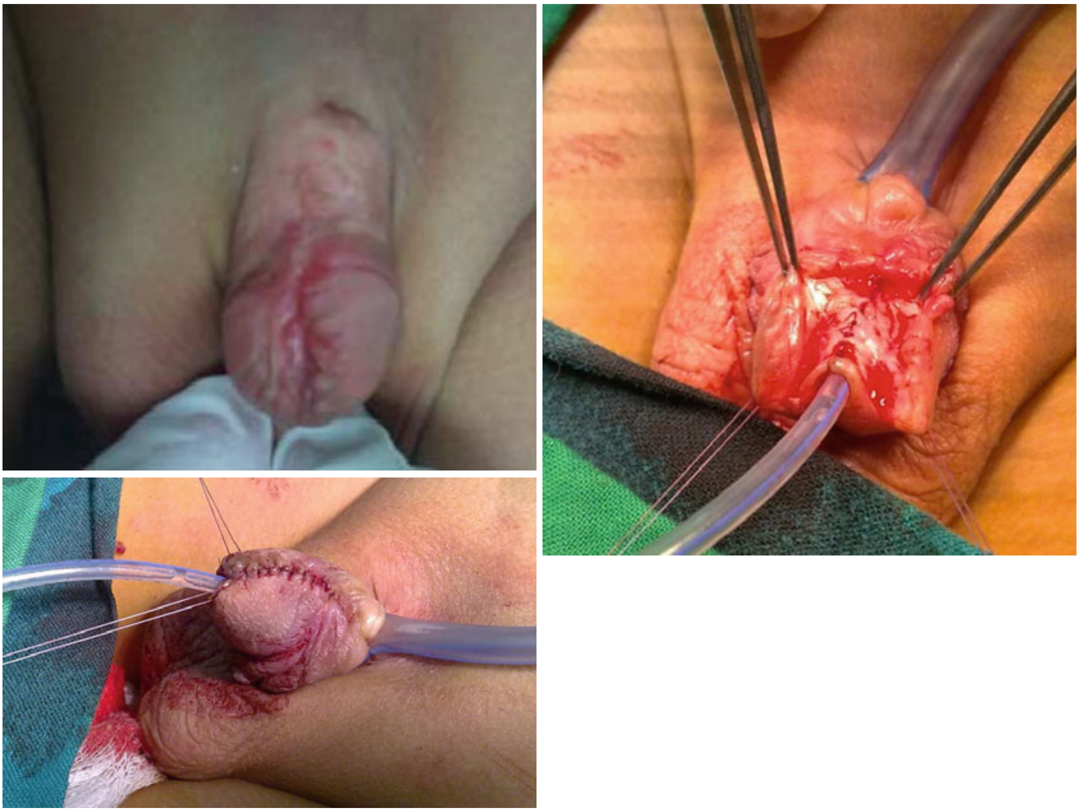
Figs. 13.31, 13.32, and 13.33 Clinical operative photographs showing repair of epispadias. Note the normal size and shape of the penis. Note also the good size and position of the urethral meatus

- They have penises that are normal in terms of shape and function.
- They are continent and do not require further surgeries.
- Their sexual function is normal and can have children.
- Those with severe degrees of epispadias may have erectile dysfunction are unable to conceive children.
- They may be incontinent and require surgeries to correct this.
- The prognosis of females with epispadias is usually excellent and their future fertility is not affected.

13.4 Bladder Exstrophy

13.4.1 Introduction

- Bladder extrophy is a rare congenital malformation.
- It is characterized by an abdominal wall defect, an open bladder and urethra with an epispadias and a wide pubic diastasis.
- The prevalence of classic bladder exstrophy is estimated to be 3.3 per 100,000 births.
- Classic bladder exstrophy is more common in males with a male-to-female ratio of 2.3:1 and as high as 6:1.
- Bladder exstrophy can present as an isolated classic bladder exstrophy or part of the cloacal exstrophy (Fig. 13.37, 13.38, 13.39, 13.40, and 13.41).
- Bladder exstrophy is the most common presentation of exstrophy-epispadias complex, occurring in approximately 1 per 10,000 to 1 per 50,000 births and affecting males approximately twice as often as females.
- The risk factors for bladder exstrophy include:
  - Caucasian race
  - Young maternal age
  - Maternal multiparity
  - Children conceived with in vitro fertilization



Figs. 13.34, 13.35, and 13.36 Clinical photographs showing a redo repair of epispadias after initial failure of the distal part of the repair

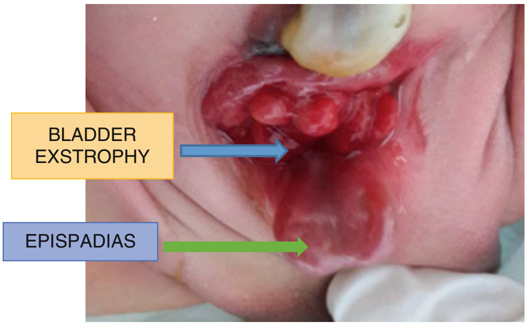


Fig. 13.37 A clinical photograph showing classic bladder extrophy. Note the open urinary bladder and the associated complete epispadias

- The diagnosis of bladder extrophy epispadias complex can be made prenatally by ultrasound.
  - This is important to council parents
  - And also to transfer these patients prior to delivery to specialized centers experienced in the management of these patients.
- Counseling should be provided to parents but, due to a favorable outcome, termination of the pregnancy is no longer recommended.
- Following reconstructive surgery of the bladder, continence rates of about 70–80 % are expected during childhood.
- Additional surgery might be needed to improve continence, bladder capacity and emptying function.
- Urinary diversion should be considered only if reconstructive surgery fails.
- Psychosocial and psychosexual outcome is important in these patient and a multidisciplinary team approach is essential in this regard.
- If the patient's bladder capacity does not increase sufficiently following closure, the patient may ultimately need augmentation cystoplasty.
- In cases when the bladder is excessively fibrotic or is too small even to attempt augmentation, then bladder substitution surgery, in the form of orthotopic neobladder or a

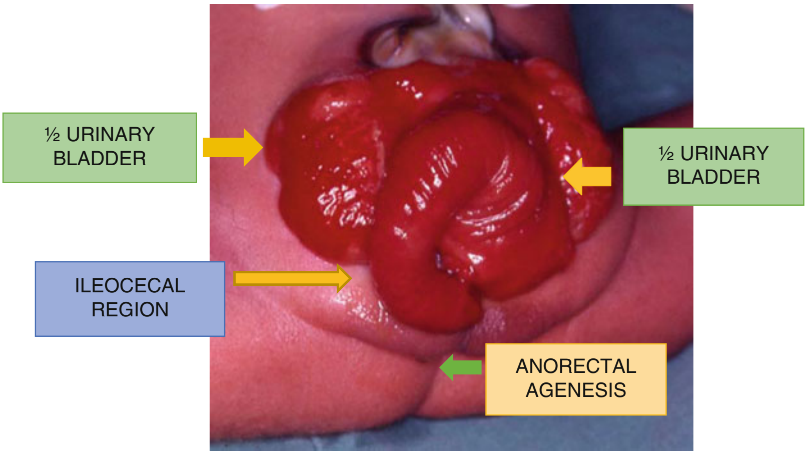
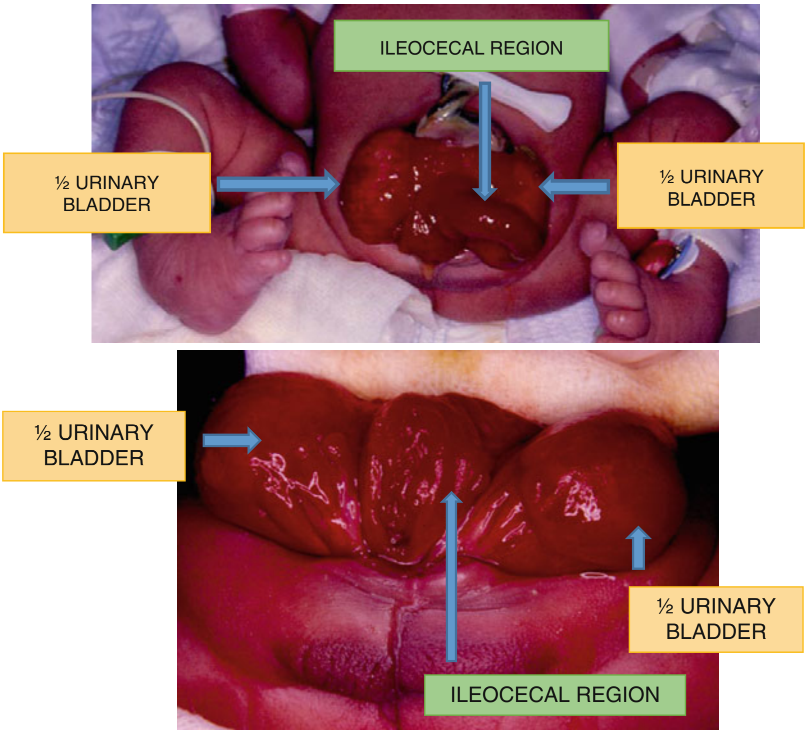

½ URINARY BLADDER
½ URINARY BLADDER
ILEOCECAL REGION
ANORECTAL AGENESIS

Fig. 13.38 A clinical photograph showing bladder exstrophy as part of the cloacal exstrophy. Note the urinary bladder divided into two parts and the space between them is occupied by the prolapsed ileocecal region. Note also the associated anorectal agenesis


ILEOCECAL REGION
½ URINARY BLADDER
½ URINARY BLADDER
½ URINARY BLADDER
½ URINARY BLADDER
ILEOCECAL REGION

Figs. 13.39 and 13.40 Clinical photographs showing bladder exstrophy as part of the cloacal exstrophy. Note the widely separated two halves of the bladder. Note also the prolapsing ileocecal region between the two halves of the urinary bladder. Note also the associated anorectal agenesis and bilateral club feet

continent catheterizable pouch, is generally undertaken.

- Reconstruction of exstrophy-epispadias complex remains one of the greatest challenges facing the pediatric surgeons and pediatric urologist.
- The goals of treatment include:
  - Closing the defect in the urinary bladder
  - Closing the abdominal wall defect while maintaining renal function
  - Achieving urinary continence
  - Maintaining sexual function
  - Achieving cosmetically and functionally acceptable external genitalia
  - Creation of a neo-umbilicus
- Repair of bladder exstrophy can be done in one of two procedures:
  - Staged functional closure for classic bladder exstrophy:
    - The bladder closure is completed within 72 h of birth.
    - If this is delayed, pelvic osteotomies are required to facilitate successful closure of the abdominal wall and to allow the

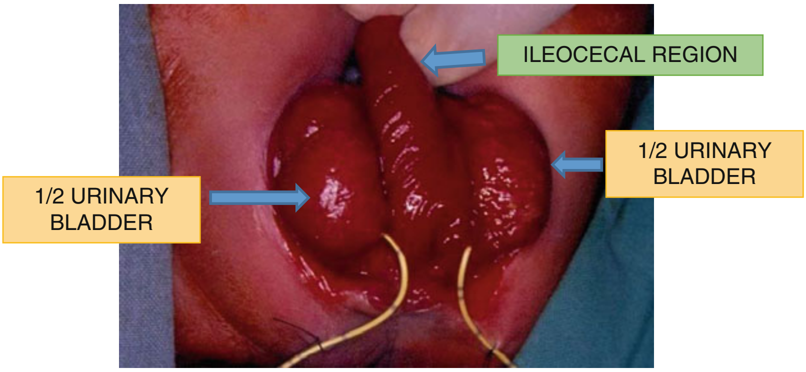


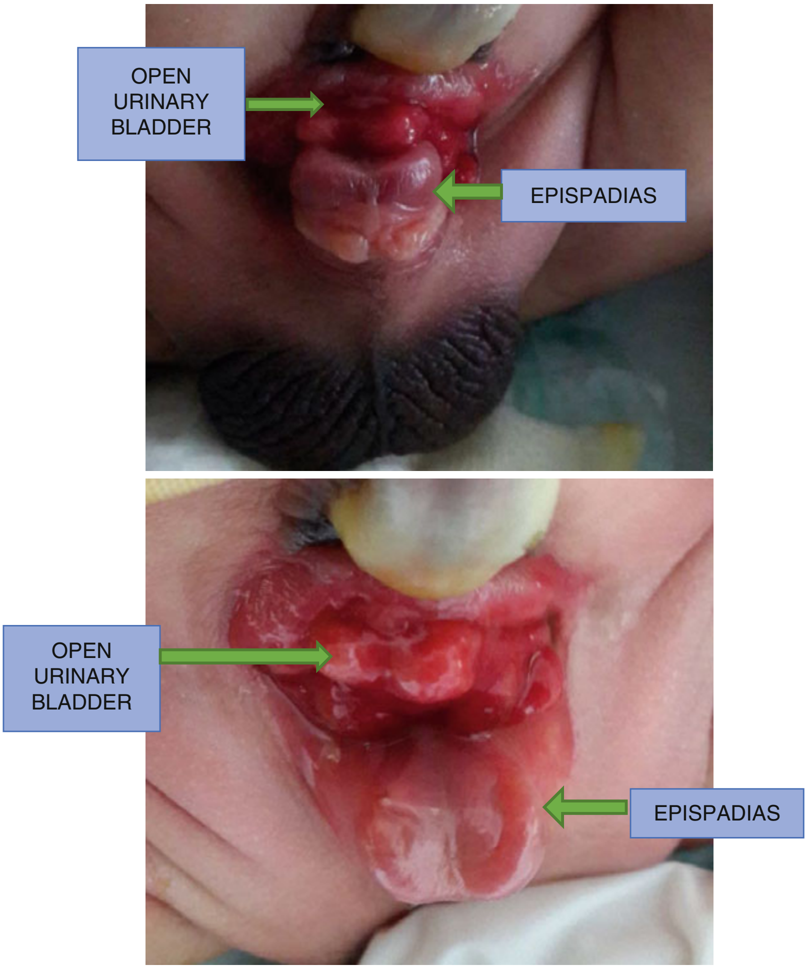
Fig. 13.41 A clinical photograph showing bladder exstrophy as part of the cloacal exstrophy. Note the two halves of the urinary bladder with stents in the two ureters

bladder to lie within a closed and supportive pelvic ring.

  - Epispadias repair with urethroplasty is delayed till age 12–18 months. This allows enough increase in bladder outlet resistance and improve the bladder capacity.
  - Bladder neck reconstruction is done at age 4 years
  - A modified Young-Dees-Leadbetter repair is preferred. Multiple modifications of this have been proposed.
  - This allows continence and correction of vesicoureteral reflux.
- – Complete primary repair for classic bladder exstrophy
  - Primary bladder closure, urethroplasty, and genital reconstruction are performed in a single stage in newborns.
  - This procedure involves complete penile disassembly in males and mobilization of the urogenital complex in females.
  - Hypospadias is a common outcome in males and this requires subsequent urethroplasty.

- Classic bladder exstrophy is characterized by:
  - – The bladder is open to the outside on the lower abdomen.
  - – The abdominal wall appears long because of a low-set umbilicus on the upper edge of the bladder plate.
  - – The distance between the umbilicus and anus is foreshortened.
  - – The pubic symphysis is widely separated.
  - – The rectus muscles diverge distally, attaching to the widely separated pubic bones.
  - – Indirect inguinal hernias are frequent (>80 % of males, >10 % of females) due to wide inguinal rings and the lack of an oblique inguinal canal.
  - – In males with classic bladder exstrophy (Figs. 13.42, 13.43, 13.44, and 13.45):
    - The phallus is short and broad with upward curvature (dorsal chordee).
    - The glans lies open and flat.
    - The dorsal component of the foreskin is absent.
    - The urethral plate is open and extends the length of the phallus.
    - The bladder plate and urethral plate are in continuity, with the verumontanum and ejaculatory ducts visible within the prostatic urethral plate.
    - The anus is anteriorly displaced with a normal sphincter mechanism.
  - – In females with classic bladder exstrophy:
    - The clitoris is bifid with divergent labia superiorly.
    - The open urethral plate is in continuity with the bladder plate.
    - The vagina is anteriorly displaced. The anus is anteriorly displaced with a normal sphincter mechanism.
- Radiological evaluation:
  - – A baseline abdominal ultrasound is important in these patients because increased bladder pressure after bladder closure can lead to hydronephrosis.
  - – Bilateral vesicoureteral reflux is common and seen in nearly all patients with classic bladder exstrophy.

Figs. 13.42 and 13.43 Clinical photographs of a male with classic bladder exstrophy. Note the small size of the open urinary bladder and the associated epispadias. Note also the phallus which is short, wide with dorsal chordee


OPEN URINARY BLADDER
EPISPADIAS
OPEN URINARY BLADDER
EPISPADIAS

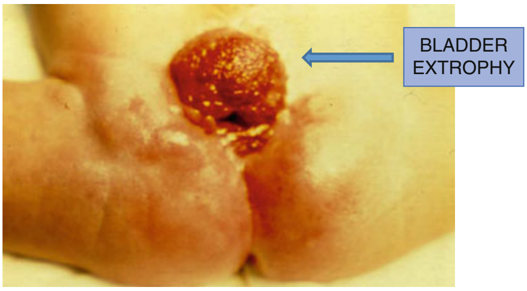

BLADDER EXTROPHY

Fig. 13.44 A clinical photograph of a female with bladder extrophy. Note the small size of the urinary bladder with granular appearance

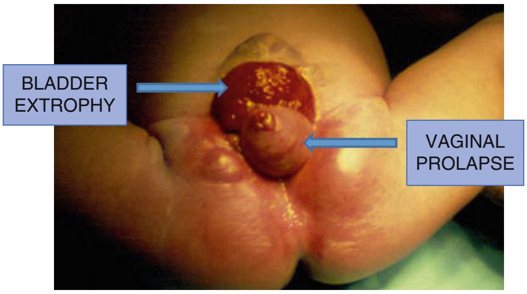

BLADDER EXTROPHY
VAGINAL PROLAPSE

Fig. 13.45 A clinical photograph showing bladder exstrophy in a female. Note also the associated vaginal prolapse

13.4.2 Associated Anomalies

- Associated anomalies are common in patients with cloacal extrophy-epispadias complex.
- The ureters in bladder extrophy and cloacal extrophy patients enter the bladder at an abnormal angle leading to vesicoureteral reflux in all patients following bladder closure. The ureters are most commonly

  reimplanted into the bladder at the time of augmentation or bladder neck reconstruction in staged repair. They can also be safely reimplanted during primary complete repair.
- Common urological anomalies include ureteropelvic junction obstruction, horseshoe kidney, and ectopic kidney.
- The pelvic deformities may cause the child to ambulate with a waddling gait.
- Magnetic resonance imaging (MRI) studies have shown that the pelvic floor musculature is also significantly different in patients with extrophy-epispadias complex. Cloacal extrophy patients have similar, but more severe, pelvic floor musculature abnormalities than bladder extrophy patients. These deficits contribute to incontinence in these patients and predispose females to vaginal and uterine prolapse.
- Gastrointestinal Abnormalities
  - An anteriorly displaced anus and anal sphincter is found in patients with bladder extrophy.
  - Bladder extrophy patients occasionally have omphalocele, imperforate anus, rectal stenosis, and rectal prolapse.
  - Cloacal extrophy patients almost always have some gastrointestinal defect. These include omphalocele, imperforate anus, rudimentary hindgut, malrotation of the bowel, and short gut syndrome, the last of which is often compounded by multiple bowel surgeries.
- Neurospinal Abnormalities
  - Approximately 7 % of bladder extrophy patients will have a spinal abnormality such as spina bifida occulta, scoliosis, and hemivertebrae.
  - Spinal dysraphism may cause neurologic dysfunction.
  - Nearly all cloacal extrophy patients demonstrate significant neurospinal deficits including:
    - Neural tube defects
    - Vertebral anomalies
    - Spinal myelodysplasia
    - Spinal dysraphism
    - Tethered cord
  - These associated anomalies necessitate prompt neurological evaluation with spinal US and MRI and can further exacerbate urinary and bowel incontinence, lower extremity immobility, and erectile dysfunction.

13.4.3 Principles of Surgical Management of Bladder Exstrophy

- The surgical technique of staged repair of classic bladder exstrophy include:
  - Initial bladder closure is completed within 72 h of birth.
  - If bladder closure is delayed, pelvic osteotomies are required to facilitate successful closure of the abdominal wall and to allow the bladder to lie within a closed and supportive pelvic ring.
  - Performance of anterior innominate osteotomy allows approximation of the pubic bones, closure of the symphysis pubis and abdominal wall muscles without tension.
  - This is performed in conjunction with pediatric orthopedic surgeons.
  - The urinary bladder is drained via a suprapubic tube or a urethral catheter and ureteral stents are also left in place.
  - At the end of the first stage procedure, the patient will be left with an epispadias.
  - Repair of epispadias is delayed till the age 12–18 months to allow time to improve bladder capacity.
  - The epispadias repair is performed using the modified Cantwell-Ransley repair technique.
  - The bladder neck is reconstructed at the age of 4–8 years.
  - Bladder neck reconstruction is done using the modified Young-Dees-Leadbetter repair. This allows correction of associated vesico-ureteral reflux.
  - The procedure is delayed until bladder capacity is adequate.
  - It has been reported that the results are much better with a bladder capacity greater than 85 ml.

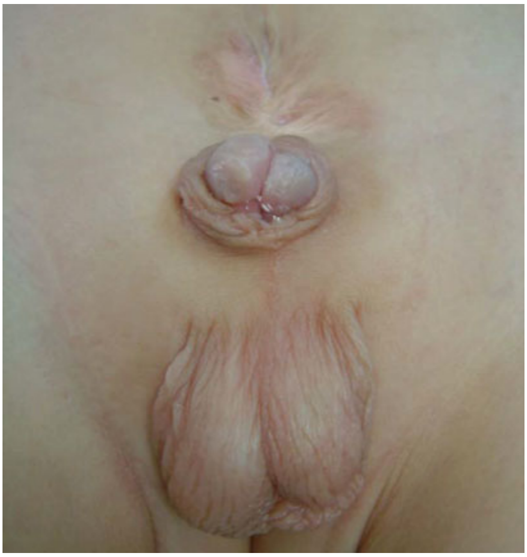


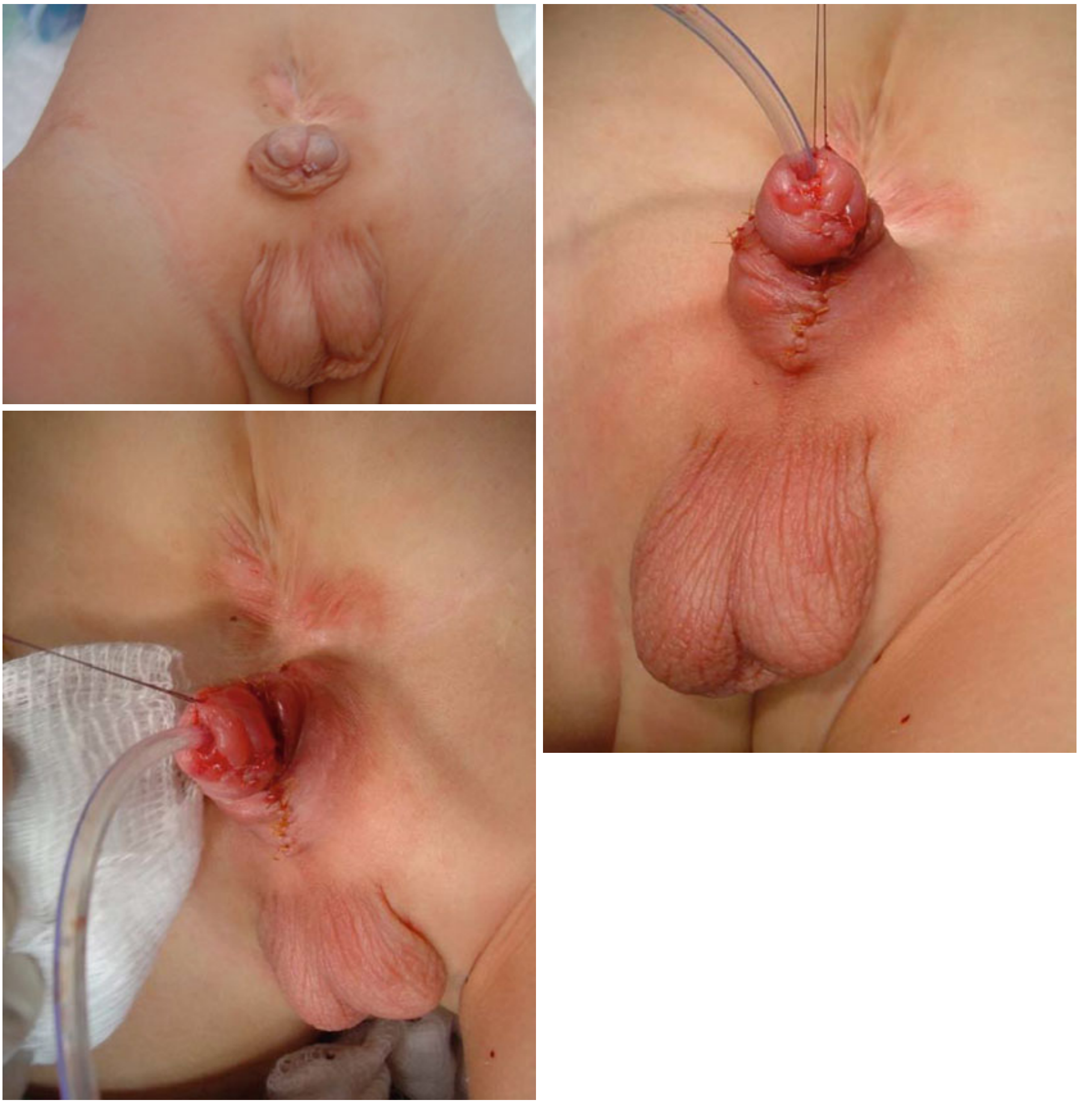
Fig. 13.46 A clinical photograph showing the end result after staged repair of classic bladder exstrophy. Note the scar of bladder closure. Note also the small phallus with epispadias which needs to be repaired in the second stage

- The surgical technique of complete primary repair for classic bladder exstrophy:
  - In this technique, bladder closure, epispadias repair, and genital reconstruction are performed in a single stage in the newborn period.
  - Hypospadias is a common outcome in males postoperatively and requires subsequent urethroplasty (Fig. 13.46).

13.4.4 Evaluation and Management

- It is important to tie the umbilical cord immediately after delivery with 2.0 silk as the umbilical clamp causes irritation and trauma to the open urinary bladder.
- The bladder mucosa should be frequently irrigated with warm saline and always covered with a protective clear plastic wrap that is changed at frequent intervals until the time of bladder closure. Avoid using wet gauze which can cause irritation to the delicate bladder mucosa.
- The treatment of bladder exstrophy-epispadias is complex should be performed in specialized centers and by experienced surgeons. The reconstructive surgery consists of a series of corrective surgeries performed over several years.
- The management of these patients should be in specialized centers and via a multidisciplinary approach which include:
  - Neonatologist
  - Pediatric gastroenterologist
  - Pediatric urologist or pediatric surgeon with special interest and expertise in the management of exstrophy-epispadias complex
  - Neurosurgeon
  - Pediatric Orthopedic surgeon
  - Child psychiatrist
  - Stoma therapist
  - Social workers
- The parents stress should not be overlooked during the initial and long-term care of these patients.
- A cardiac echo is commonly done to rule out significant cardiopulmonary anomalies.
- A renal ultrasound should be obtained to evaluate the upper urinary tracts.
- A KUB is done to evaluate the pelvis bony anatomy.
- A spinal ultrasound is done to rule out an associated spinal dysraphism.
- Antibiotics should be started immediately after delivery and continued postoperatively.
- Daily prophylactic antibiotic therapy should be given to these patients during postoperative follow-up.
- These patients have a high incidence of latex sensitization and it is important to institute latex precautions.
- The goals of treatment include:
  - Closing the defect in the urinary bladder
  - Closing the abdominal wall defect while maintaining renal function
  - Achieving urinary continence and adequate urinary storage at low pressures with the ability to empty the bladder completely without compromising renal function.
  - Maintaining sexual function.
  - Achieving cosmetically and functionally acceptable external genitalia.
  - Creation of a neo-umbilicus

- In the past, early attempts at bladder exstrophy repair were unsuccessful and for many years the management for bladder exstrophy consisted of excision of the exstrophic bladder and urinary diversion commonly by ureterosigmoidostomy.
- The surgical management of bladder exstrophy has changed over the years and many modifications in surgical techniques have improved the outcome for these patients.
- Currently, most patients are managed either with:
  - A (single stage) complete primary repair of bladder exstrophy (Mitchell technique).
  - Or modern staged reconstruction of exstrophy.
- There are those who advocate a staged approach while others prefer total reconstruction in one stage.
- Early bladder closure (closure during the first 72 h) is beneficial.
  - It decreases inflammation and fibrosis of the bladder
  - Improves bladder growth and expansion
  - Decreases the need for urinary diversion
  - Decreases the risk of precancerous changes in the bladder
- Pelvic osteotomies:
  - Pelvic osteotomies may be performed at the time of primary closure.
    - This helps deepen the flattened pelvis
    - Close the pubic diastasis
    - Release tension on the abdominal wall
  - Pelvic osteotomies are recommended in patients who undergo repair after 72 h of age as this facilitates closure of the bladder and abdominal wall and also results in deeper placement of the bladder into the pelvis.
  - A combination of bilateral anterior transverse innominate and vertical posterior iliac osteotomies has been shown to decrease the rate of abdominal dehiscence and bladder prolapse.
  - There are several maneuvers to facilitate this including:
    - The use of fixator pins and external fixation devices can be placed and left postoperatively for 4–6 weeks.
    - Modified Buck's traction exerts pull longitudinally on the lower extremities.
    - Modified Bryant's traction, where the hips are placed into 90° of flexion, may be used if there is no osteotomy.
    - Spica casts to immobilize the pelvis without the need for external fixators or traction.
    - "Mummy wrapping" the child's legs.
- Complete Primary Repair of Exstrophy (CPRE):
  - This technique was pioneered by Dr. Mitchell in 1996.
  - The CPRE is done as a one stage procedure with or without pelvic osteotomies and includes:
    - Bladder closure with bladder neck remodeling.
    - A disassembly technique for epispadias repair.
    - This technique allows for bladder cycling and more 'normal' growth and development because the bladder experiences an outlet resistance.
    - The disassembly technique for epispadias repair also allows for division of the intersymphyseal ligaments and appropriate anatomic placement of the bladder neck and posterior urethra deep into the pelvis in its normal position.
    - If the procedure is done within the first 72 h of life, the pelvis is malleable enough to close without osteotomies.
    - Postoperatively, the patient is placed in Bryant's traction for approximately 1 week and then lower extremity casting for 3 weeks to prevent tension on the pelvis closure.
    - A large number of these patients require a formal bladder neck procedure to achieve continence
  - Outcome and complications of CPRE:
    - The outcome of CPRE is generally good.
    - Continence defined as dry intervals longer than 2 h and spontaneous voiding without catheterizations is around 75 %.



Figs. 13.47, 13.48, and 13.49 Clinical photographs showing repair of hypospadias following closure of classic bladder exstrophy and epispadias repair. Note the scar following closure of the urinary bladder

- About 30 % of these patients require clean intermittent catheterization (CIC).
- There is a potential risk for renal deterioration related to a high pressure lower urinary system in these patients
- Glans necrosis and penile injury or loss.
- Hydronephrosis, pyelonephritis and renal scarring.
- Approximately 36–68 % of patients will be left with a hypospadias that will require urethroplasty (Figs. 13.47, 13.48, and 13.49).
- Modern Staged Reconstruction of Exstrophy (MSRE):
  - In this technique, the exstrophic bladder is closed first.
  - A pelvic osteotomy will facilitate this closure as well as closure of the abdominal wall. This is especially so if the closure is performed after 72 h of birth.
  - The end result is a complete epispadias.
  - The epispadias repair is performed between 6 and 12 months of age.
  - Penile growth can be stimulated with long acting testosterone.

  - The bladder neck repairs for continence is performed between 4 and 5 years of age if they have an adequate bladder capacity.
  - This can be delayed until the bladder grows and maturity improves.
  - The other alternative is bladder augmentation with a catheterizable channel and bladder neck closure when necessary.
  - Outcome and complications:
    - Continence rates are reported to be 70 % in males and 74 % in females with dry periods greater than 3 h with spontaneous voiding and dry at night without clean intermittent catheterization.
    - A bladder capacity of 100 ml predicts success at the time of bladder neck reconstruction utilizing the modified Young-Dees-Leadbetter repair.
    - If the bladder capacity is less than 100 ml, these patients should undergo an augmentation at the time of reconstruction for continence.
- Bladder neck reconstruction:
  - This allows continence and correction of vesicoureteral reflux.
  - The procedure is delayed until bladder capacity is adequate; better results are reported with a bladder capacity greater than 85 ml.
  - A continence procedure such as the Young-Dees-Leadbetter, is delayed until the patient achieves a bladder with adequate capacity and desires continence (usually between 5 and 9 years of age).
  - This stage is combined with ureteral reimplantation to repair associated vesicoureteral reflux.
  - Children who are not candidates for a continence procedure or who fail to achieve urinary continence after the procedure may require bladder neck transection, augmentation cystoplasty, and continent catheterizable stoma.
  - This will make clean intermittent catheterization (CIC) to empty their bladders easier.
- Bladder Augmentation:
  - This is indicated for patients with a bladder that is noncompliant or of insufficient capacity.
  - Several techniques using segments of bowel, stomach, or redundant ureter have been used to augment the bladder.
  - Following augmentation cystoplasty, a continent urinary diversion is performed using a segment of appendix or ileum.
  - This segment connect the urinary bladder to the abdominal wall and provide a continent stoma through which to perform clean intermittent catheterization.
  - This makes clean intermittent catheterization much easier for these patients and more convenient.
- In females, the external genitalia are fully reconstructed at the time of exstrophy closure.
  - This includes reapproximation of the bifid clitoris and anterior labia to make a fourchette.
  - A monsplasty is an important part of reconstruction in females using hair bearing skin and fat to cover the midline defect.
  - Further reconstruction is done during adolescent years including total urogenital mobilization to correct the location and angle of the vagina in female exstrophy patients.
  - These patients usually have normal sexual desire and normal sexual intercourse after reconstruction.
  - These patients can subsequently become pregnant and deliver normally.
  - There is however an increased risk of vaginal, cervical and uterine prolapse in these patients. This is especially seen after pregnancy and delivery.
  - It is recommended that these patients should undergo cesarean sections to eliminate stress on the pelvic floor and to avoid traumatic injury to the urinary sphincter mechanism.
- Male patients with exstrophy have normal sexual function and libido but are at high risk of infertility after reconstruction. These patients can be helped further with an assisted reproduction.
- Currently, 70–75 % of patients with bladder exstrophy are continent following modern reconstruction.

- Postoperative complications include:
  - Bladder Prolapse
  - Bladder outlet Obstruction
  - Vaginal prolapse
  - Bladder Calculi
  - Renal Calculi
  - Wound Dehiscence including urethra and bladder dehiscence
  - Hypospadias

13.5 Cloacal Exstrophy

13.5.1 Introduction

- Cloacal exstrophy is an extremely rare birth defect with an estimated prevalence at around 1 in 50,000–200,000 live births (Fig. 13.50).
- It is more common in males than females (a male-female sex ratio of 2:1).
- Cloacal exstrophy (EC) is a major birth defect representing the severe end of the spectrum of the exstrophy-epispadias complex. It is characterized by the presence of:
  - Omphalocele
  - Bladder exstrophy
  - Imperforate anus
  - Spinal defects
- The size of omphalocele is variable.
- It is also called vesico intestinal fissure.
- To include the components of cloacal exstrophy, it is also called the OEIS Complex:
  - O: Omphalocele
  - E: Exstrophy of the cloaca
  - I: Imperforate Anus
  - S: Spinal Defects
- Clinically, patients with cloacal exstrophy present at birth and the followings form the spectrum of anomalies that are related to cloacal exstrophy (Figs. 13.51, 13.52, 13.53, 13.54, and 13.55):
  - Two exstrophied hemi bladders
  - These are separated by a foreshortened hindgut or cecum
  - The hindgut is often blind-ending resulting in an imperforate anus. This extrophied ileo-cecal region presents between the two hemi bladders (the “elephant trunk” appearance).
  - Omphalocele
  - Malrotation of bowel
  - The symphysis pubis is widely separated
  - The pelvis is often asymmetrically shaped
  - The genitalia (ambiguous genitalia):
    - The penile or clitoral halves are usually located separately on either side of the bladder plates with the adjacent scrotal or labial part.
    - Duplication of the vagina and uterus
    - Vaginal agenesis

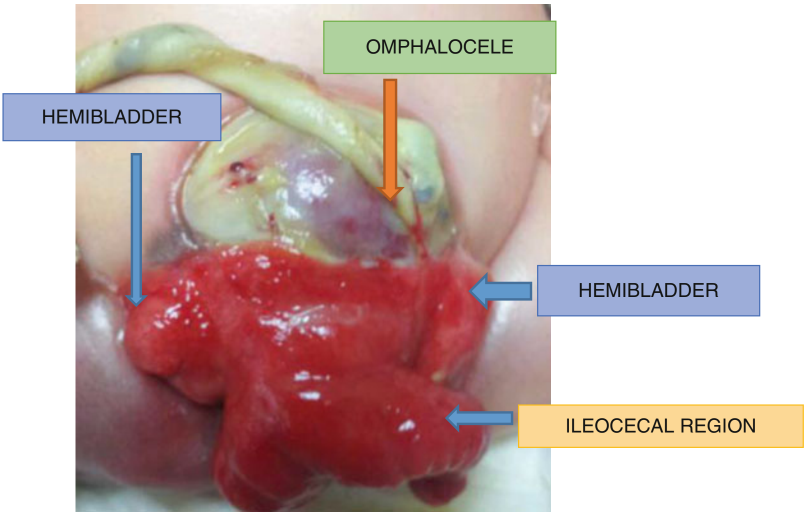
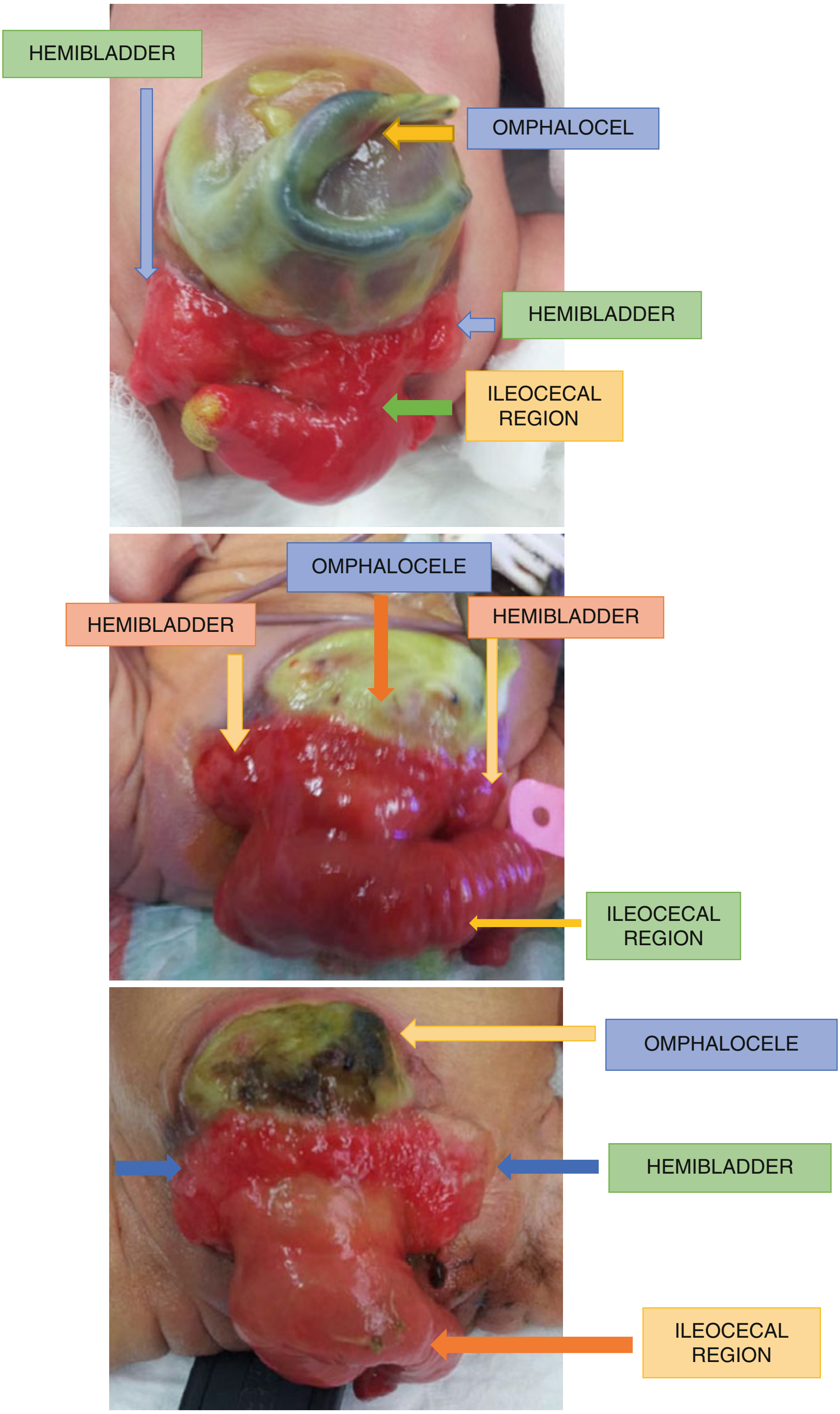
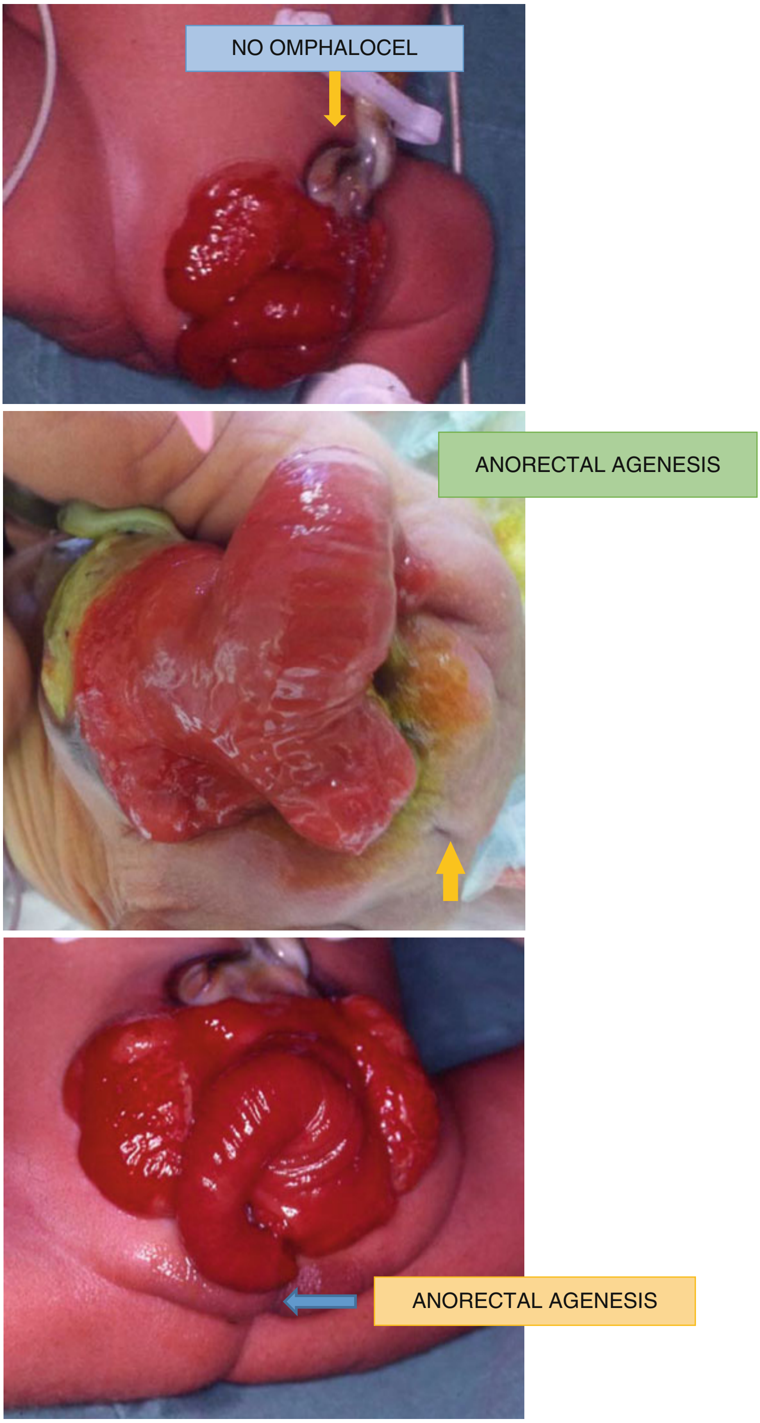


Fig. 13.50 Clinical photograph showing the components of the cloacal exstrophy


HEMIBLADDER
OMPHALOCEL
HEMIBLADDER
ILEOCECAL REGION
OMPHALOCELE
HEMIBLADDER
HEMIBLADDER
ILEOCECAL REGION
OMPHALOCELE
HEMIBLADDER
ILEOCECAL REGION

Figs. 13.51, 13.52, and 13.53 Clinical photographs showing two patients with cloacal exstrophy. Note the difference in the size of omphalocele and also the extent of the exstrophied ileocecal region


NO OMPHALOCEL
ANORECTAL AGENESIS
ANORECTAL AGENESIS

Figs. 13.54, 13.55, and 13.56 Clinical photographs showing cloacal exstrophy in three patients. Note the absence of omphalocele in the first one and associated anorectal agenesis in the other two patients

- Bladder Exstrophy-Epispadias Complex represents a spectrum of genitourinary malformations ranging in severity from epispadias and classical bladder exstrophy to cloaca exstrophy. Add to this the exstrophy variants. Among these, cloacal exstrophy is the most severe (Fig. 13.56).
- Cloacal exstrophy is characterized by malformations of the gastrointestinal, musculoskeletal, and central nervous systems. Classically, a portion of cecum or hindgut separates the two open hemi bladders.
- Three-dimensional CT is valuable to evaluate the bony pelvis and pelvic floor in these patients.
- Antenatal imaging demonstrating absence of bladder filling, a low-set umbilicus, widened pubic rami, small genitalia, and a lower abdominal mass that increases throughout the duration of pregnancy may indicate bladder exstrophy or cloacal exstrophy.
- The prolapsed ileum in cloacal exstrophy patients may look like an “elephant trunk appearance” on antenatal ultrasound.
- Delivery of these patients should be arranged at a specialized medical center with expertise in managing this complex anomaly. Similarly, infants who are diagnosed at birth should be promptly transported to such centers to allow for an experienced evaluation and possibly primary closure.

13.5.2 Skeletal Changes in Cloacal Exstrophy

- Separation of the pubic bones
- Outward rotation of the innominate bones
- Eversion of the pubic rami
- A 30 % shortage of bone in the pubic ramus
- External rotation of the posterior aspect of the pelvis
- Retroversion of the acetabulum
- External rotation of the anterior pelvis
- The sacro-iliac joint angle is 10-degrees larger in the exstrophy pelvis compared to age-matched controls and 10-degrees more toward the coronal plane than sagittal.
- The bony pelvis is 14.7-degrees inferiorly rotated.
- The sacrum was 42.6 % larger by volume measurements and had 23.5 % more surface area.
- These deformities of the pelvic bones contribute to the shortened phallus, waddling gait, and outward rotation of the lower limbs in exstrophy patients.
- Spina bifida occulta
- Lumbarization or sacralization of vertebrae
- Uncomplicated scoliosis
- Spinal dysraphism including myelomeningocele, lipomeningocele, scimitar sacrum, and hemivertebrae.

13.5.3 Etiology and Pathogenesis

- The exact etiology of cloacal exstrophy is not known.
- Several theories have been proposed to explain the pathogenesis of cloacal exstrophy but none of them can fully explain the spectrum of anomalies seen in cloacal exstrophy.
- The most accepted theory is that cloacal exstrophy results from premature rupture of the cloacal membrane prior to caudal migration of the urorectal septum, and failure of fusion of the genital tubercles.
- Embryo logically:
  - The urorectal septum divides the cloaca into an anterior urogenital sinus and a posterior anorectal canal.
  - This occurs around the fourth week of intrauterine life and simultaneously, the cloacal membrane is invaded by lateral mesodermal folds.
  - It is postulated that if this mesodermal invasion does not occur, the infraumbilical cloacal membrane persists leading to poor lower abdominal wall development.
  - The cloacal membrane eventually ruptures but if this happens prior to the descent of the urorectal septum which happens at 6–8 weeks of gestation, then cloacal extrophy results.

- Cloacal extrophy develops as a result of:
  - Failure of the urorectal septum to develop and divides the urogenital sinus anteriorly from the rectum posteriorly.
  - Failure of the mesoderm forming the infraumbilical abdominal wall to proliferate and form the lower abdominal wall
  - Failure of the genital tubercle to develop.
  - Failure of these events to occur results in exstrophy of both bladder and intestine.
- Classically, cloacal exstrophy is made up of omphalocele, exstrophied ileocecal region of bowel, exstrophied hemi bladders each with its ipsilateral ureter, and anorectal agenesis.
- The pubic bones are widely separated, and spinal dysraphism is common in these patients.

13.5.4 Prenatal Diagnosis

- The prenatal diagnosis of cloacal exstrophy is now possible based on prenatal ultrasound findings.
- The prenatal ultrasound findings were classified into major and minor criteria.
- The Major criteria include:
  - Nonvisualization of the urinary bladder (91 %)
  - A large midline infraumbilical anterior wall defect or a cystic anterior wall structure (82 %)
  - An omphalocele (77 %)
  - A myelomeningocele (68 %)
- The minor criteria include:
  - Lower extremity anomalies (23 %)
  - Renal anomalies (23 %)
  - Ascites (41 %)
  - Widened pubic arches (18 %)
  - Narrow thorax (9 %)
  - Hydrocephalus (9 %)
  - A single umbilical artery (9 %)
  - The characteristic elephant trunk appearance that the prolapsing terminal ileum can produce

13.5.5 Associated Anomalies

- Cloacal exstrophy is commonly associated with other anomalies including cardiovascular, and central nervous system anomalies.
- Omphalocele (70–90 %)
- Spinal and Skeletal Anomalies (46 %):
  - The pelvic defects in cloacal exstrophy are similar in nature but more severe than that in bladder exstrophy.
  - The interpubic diastasis is wide.
  - The anterior segment length (distance from the triradiate cartilage to the pubis) is shorter in cloacal exstrophy patients.
  - The angle of iliac wing is markedly increased showing extreme external rotation.
  - The ischiopubic angle is increased.
  - Asymmetry between the pelvis sides, sacroiliac joint malformations, and occasional hip malformations
  - Skeletal and limb anomalies were reported in 12–65 % of cases of cloacal exstrophy.
    - Clubfoot deformities (Fig. 13.57)
    - Absence of feet
    - Severe tibial or fibular deformities
    - Congenital hip dislocations
  - Hemivertebra
  - Myelomeningocele

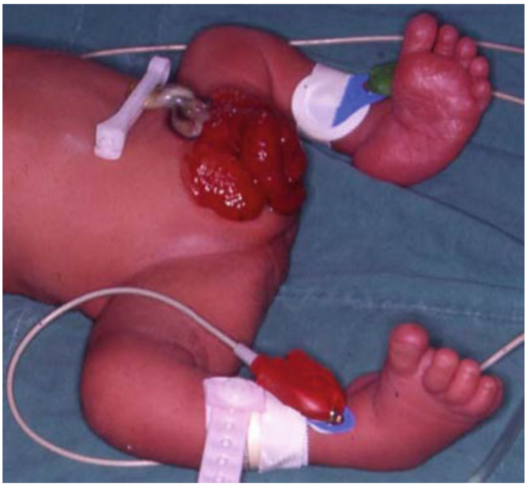
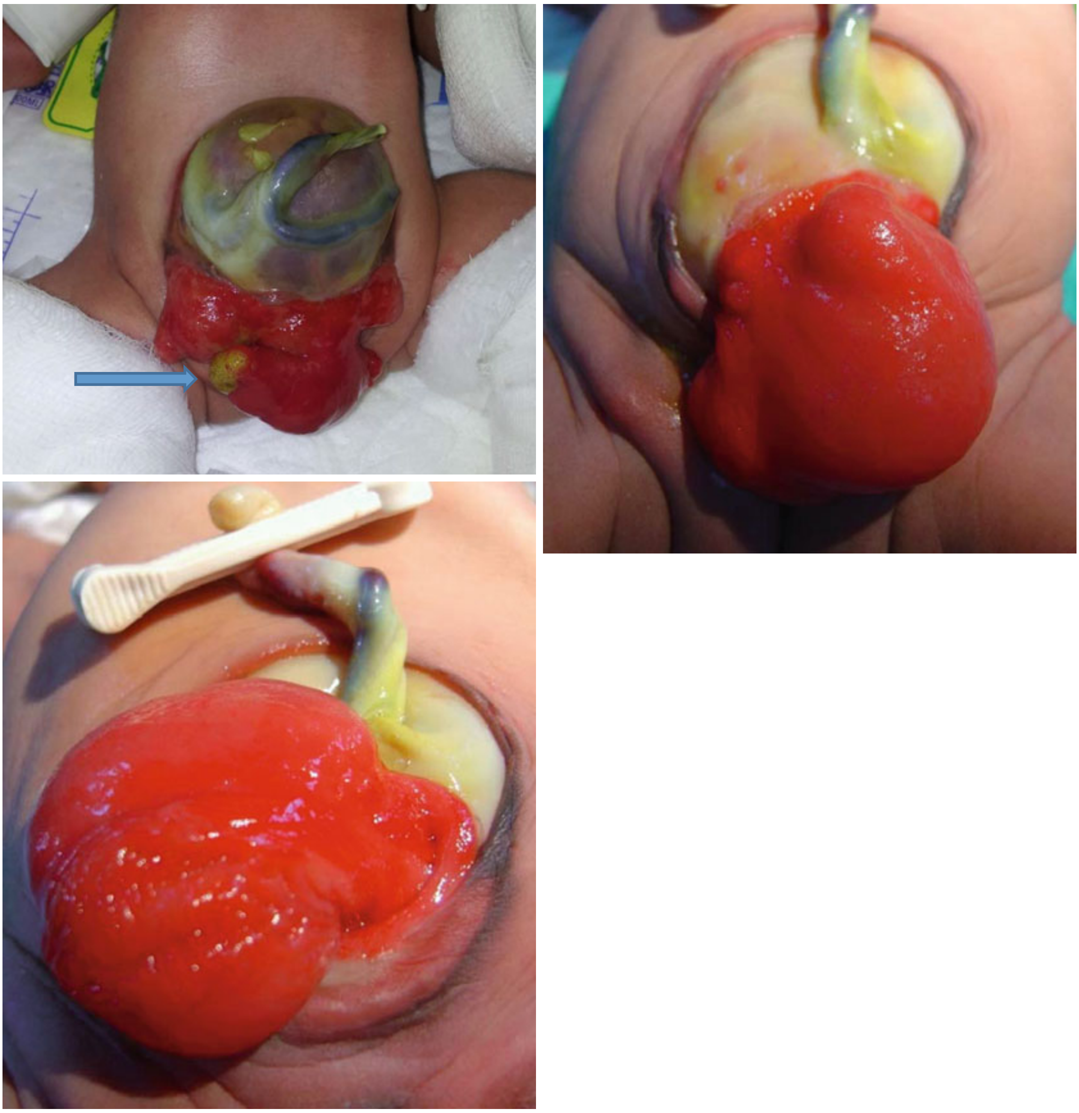


Fig. 13.57 Clinical photograph of a newborn with cloacal exstrophy. Note also the bilateral tallipes equinovarus

  - Absence of feet
  - Sacralization of L5
  - Congenital scoliosis
  - Sacral agenesis
  - Interpedicular widening
- Upper Urinary Tract Anomalies:
  - Upper tract anomalies are seen in 41–60 % of patients with cloacal exstrophy.
  - These anomalies include:
    - Ectopic Pelvic kidneys
    - Horseshoe kidney
    - Renal agenesis
    - Hydronephrosis and hydroureter
    - Multicystic dysplastic kidneys
    - Hypoplastic kidney or renal agenesis
    - Ectopic ureters
    - Ureteral duplication
    - Congenital stricture
    - Megaureters
    - Solitary kidney
    - Ureteropelvic junction obstruction
    - Ureterocele
- Lower extremity anomalies (30 %)
- Double appendix (30 %)
- Absent appendix (21 %)
- Short bowel syndrome (19–46 %)
- Gastrointestinal duplications
- Small bowel atresia (5 %)
- Abdominal wall musculature deficiency (1 %)
- Gastrointestinal Anomalies:
  - Omphaloceles are reported in more than 88–100 % of cloacal exstrophy and vary widely in size.
  - Other gastrointestinal anomalies were reported in 46 % of cloacal exstrophy patients.
    - Malrotation
    - Bowel duplication
    - Duodenal atresia
    - Duodenal web
    - Meckel's diverticulum
  - Short gut syndrome is reported in 25 % of cloacal exstrophy patients.
  - It is important to preserve as much bowel as possible in these patients.
  - Short gut syndrome can however develop in the presence of normal small bowel length suggesting an absorptive dysfunction.
- Neurospinal Anomalies:
  - Neurospinal abnormalities have been noted in 85–100 % of patients with cloacal exstrophy
    - Lumbar anomalies (80 %)
    - Thoracic anomalies (10 %)
    - Sacral anomalies (10 %)
  - Neurospinal anomalies include:
    - Lipomeningoceles
    - Myelomeningoceles
    - Spina bifida
    - Isolated cord tethering
  - It is recommended that all cloacal exstrophy patients have a spinal evaluation by ultrasound or MRI. Ultrasound is quicker, easier, and less expensive and does not require sedation and the ultrasound findings are comparable to MRI.
  - The presence of a significant neurologic deficit is associated with severe impairments and markedly decreased chance of developing continence.
  - Long-term follow-up is important in these patients since up to 33 % can have symptomatic spinal cord tethering.
- Mullerian and Testicular Anomalies:
  - The most common Mullerian anomaly reported was uterine duplication (95 %). The most common is partial duplication, predominately a bicornate uterus.
  - Duplication of the vagina (65 %)
  - Vaginal agenesis (25–50 %)
  - Undescended testes
  - Inguinal hernias
- Cardiovascular and Pulmonary Anomalies
  - Life-threatening anomalies of the cardiovascular and pulmonary systems are rare.
  - There are rare reports of patients with cyanotic heart disease, aortic duplication, vena caval duplication, bilobed lung and an atretic upper lobe bronchus.

13.5.6 Clinical Features and Management (Figs. 13.58, 13.59, and 13.60)

- Cloacal exstrophy is a very rare and complex anomaly of the urogenital tract and intestinal tract resulting in exstrophy of both bowel and bladder.
- Commonly in cloacal exstrophy, the exstrophied bowel is the ileo-cecal region with little or no large bowel distally, but there are cases where there is colonic exstrophy with sufficient large bowel length.
- A small colon usually ends blindly in the pelvis, and the terminal ileum often prolapses out of the exposed cecum.
- The presence of enough large bowel is advantageous from the reconstruction point of view and every attempt should be made to preserve every part of bowel.



Figs. 13.58, 13.59, and 13.60 Clinical photograph showing cloacal exstrophy. Note the omphalocele which is large in the first and small in the lower two pictures. Note also the urinary bladder in the first photograph divided into two halves and the prolapsed ileo-cecal region with the terminal ileum open with meconium passing from it. Note the large prolapsing ieocecal region in the lower pictures

- The exstrophied ileocecal region and in the presence of short large bowel should be preserved for reconstruction of the anorectal malformation.
- Every effort should be made to preserve all large intestines because:
  - It can be used for bladder augmentation which is necessary in the majority of these patients to increase the bladder compliance.
  - It can be used also for reconstruction of the anorectal malformation.
  - It can be used for vaginal reconstruction in those who have vaginal agenesis or those undergoing gender reassignment.
- Add to this the valuable absorptive function of the large bowel.
- Augmentation of the urinary bladder may be performed using the hindgut if enough length is available, ileum, or part of the stomach.
- In the absence of large intestine, both small bowel and stomach can be used for bladder augmentation but gastrocytoplasty was shown to be superior.
- Gender assignment is one of the difficult tasks in the management of newborns with cloacal exstrophy.
- It is important to determine early the genetic sex of the patient as this will affect the subsequent management.
- Genetic females should not raise a problem as they will be raised as females.
- In genetic males with cloacal extrophy, the phallic structures are usually small and completely bifid with insufficient phallic tissue to reconstruct an adequate penis.
- There is now general consensus that genetic males with insufficient phallus be gender reassigned as phenotypic females, and to minimize testosterone imprinting on the nervous system, this should be done in the immediate newborn period with early orchidectomy.
- Males with adequate bilateral or unilateral phallic structures should however, be raised as males.
- In the classic repair of cloacal extrophy in males an epispadias is created initially after urinary bladder closure.
- The treatment of cloacal exstrophy is complex and should be performed in specialized centers and by experienced surgeons.
- The reconstructive surgery consists of a series of corrective surgeries performed over several years.
- The management of newborns with cloacal exstrophy has progressed over the years, and now a very reasonable outcome is expected in most cases. This, however, requires a team approach including:
  - Neonatologists
  - Pediatric surgeons
  - Pediatric urologist
  - Neurosurgeons
  - Pediatric orthopedic surgeons
  - Endocrinologist
  - Geneticists
  - Psychologist
  - Social workers
  - Stoma therapist
  - Pediatric gastroenterologist
- Although there are general guidelines in managing newborns with cloacal exstrophy, after thorough evaluation of the anatomical abnormalities, the management should be individualized.
- Immediate management is directed to the medical stabilization of the infant.
- Evaluation and appropriate management of associated malformations should be undertaken.
- For infants who have few other associated malformations and are medically stable, staged closure can be considered.
- The exposed bowel and urinary bladder should be moistened with saline irrigation and covered with protective plastic dressing. Wet gauze applied on the urinary bladder should be avoided.
- Evaluation of the genitalia and gender assignment should be made by a gender assignment team, including a pediatric urologist, pediatric surgeon, pediatrician, and pediatric endocrinologist.
- Consultation of social worker, pediatric orthopedic surgeon and other disciplines should be obtained.

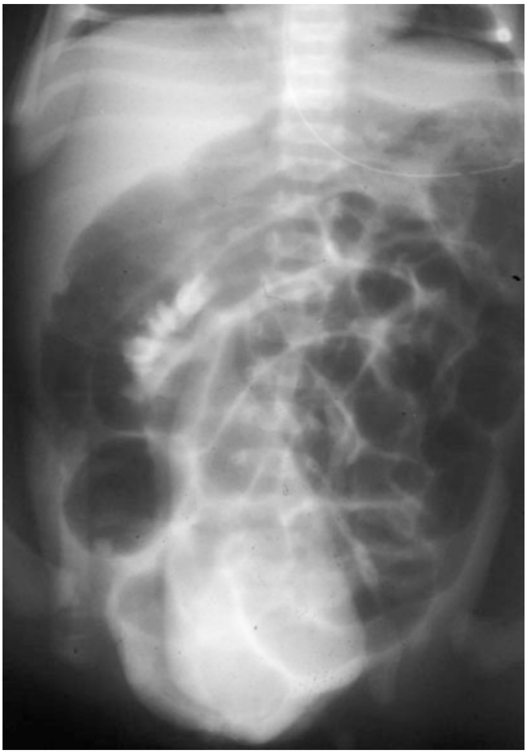


Fig. 13.61 A KUB of a patient with cloacal exstrophy. Note the soft tissue in mid lower part repressing the exstrophied bladder and ileocecal area. Note the widely separated pelvis and pubic bones

- The parents stress should not be overlooked during the initial and long-term care of these patients. A detailed discussion with the parents is important. This should include gender assignment and management plan of these patients as well as future prognosis.
- A cardiac echo is done to rule out associated cardiopulmonary anomalies.
- A renal ultrasound should be obtained to evaluate the upper urinary tracts.
- A KUB is done to evaluate the pelvis bony anatomy (Fig. 13.61).
- A spinal ultrasound or MRI is done to rule out an associated spinal dysraphism.
- Antibiotics should be started immediately after delivery and continued postoperatively.
- Daily prophylactic antibiotic therapy should be given to these patients during postoperative follow-up.
- These patients have a high incidence of latex sensitization and it is important to institute latex precautions.
- The initial operation consists of:
  - Separating the bowel from the bladder to create an intestinal stoma.
  - Closing the omphalocele.
  - Reapproximating, closing, or leaving the exstrophied bladder undisturbed.
- The importance of creating a colostomy instead of an ileostomy to prevent problems with diarrhea, dehydration, and acidosis is to be emphasized.

13.5.7 Surgical Repair of Cloacal Exstrophy (Figs. 13.62, 13.63, and 13.64)

- The surgical management of cloacal exstrophy includes:
  - Pelvic osteotomy and immobilization
  - Closure of urinary bladder
  - Closure of abdominal wall
  - An antireflux procedure
  - Augmentation cystoplasty
  - Continent urinary diversion
- After delivery, the exposed bladder and bowel mucosa should be covered or wrapped to avoid mechanical irritation. The exposed bladder is irrigated with warm normal saline.
- A spinal ultrasound or MRI is important to define and diagnose associated neurologic anomalies.
- A central line should be inserted as these patients require antibiotics and total parenteral nutrition.
- Intestinal diversion is performed along with omphalocele repair.
- It is important to preserve any rudimentary hindgut and part of bowel to avoid short bowel syndrome.
- The exposed urinary bladder is also closed.
- Gender assignment is important for those 46XY male cloacal exstrophy patients with inadequate phallic structures for reconstruction.

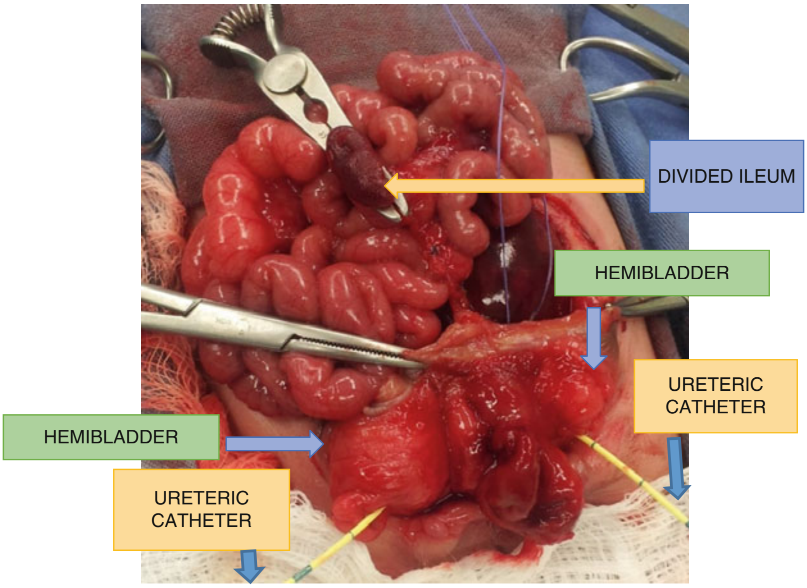
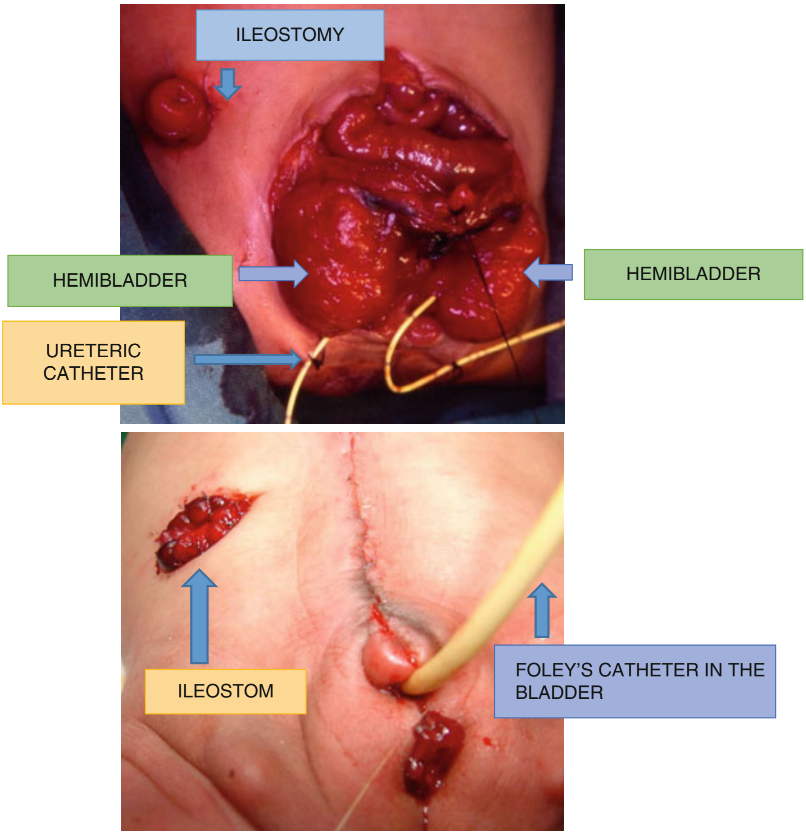

DIVIDED ILEUM
HEMIBLADDER
URETERIC CATHETER
HEMIBLADDER
URETERIC CATHETER

Fig. 13.62 A clinical intraoperative photograph of cloacal extrophy being repaired. Note the two ureteric catheters inserted and the mobilized urinary bladder. Note also the divided ileum to form an ileostomy. Part of the bowel is left in the posterior wall of the urinary bladder for bladder augmentation


ILEOSTOMY
HEMIBLADDER
HEMIBLADDER
URETERIC CATHETER
ILEOSTOM
FOLEY'S CATHETER IN THE BLADDER

Figs. 13.63 and 13.64 Clinical intraoperative and post-operative photographs showing a diverting ileostomy and a urinary catheter in the already closed urinary bladder

- It is important to discuss the gender assignment in these patients.
    - Many males with cloacal exstrophy have an unreconstructable phallus and undescended testes.
    - The parents of these patients may elect to have their son undergo a gonadectomy and be raised as a female.
    - This however may lead to possible psychosocial and behavioral outcomes of genotypic males being raised as females.
    - Currently, it is possible to reconstruct a functional and cosmetically acceptable phallus and gender assignment should be consistent with the karyotype.
    - On the other hand and as a result of advancement of surgical techniques, many are advocating for assigning gender that is consistent with karyotype, phallus reconstruction and orchidopexy.

13.5.8 Surgical Reconstruction

- Cloacal exstrophy reconstructive procedures can be done as a one-stage or two-stage.
- A one-stage closure is preferable to minimize the number of neonatal procedures and allow the bladder to be closed and protected.
- A central line should be inserted early for hydration, intravenous antibiotics and total parenteral nutrition.
- Reconstruction consists of the followings:
    - Bilateral pelvic osteotomies are performed if reconstruction is done after the first 72 h of life.
    - The omphalocele is excised.
    - The bowel is separated from the hemi bladders and care should be taken to preserve the bowel length as much as possible to avoid a short bowel.
    - The lateral vesicointestinal fissure is closed in continuity
    - A short colostomy is created from the end of the distal colon segment and an ileostomy should be avoided as much as possible.
    - The appendix should be preserved for possible later continent stoma construction if necessary.
    - The hemi bladders are then re-approximated in the midline to create a single exstrophic bladder (classic bladder exstrophy).
    - If a one-stage is selected, the entire bladder is closed completely.
    - In patients with spinal dysraphism and myelocystocele, a closure by a neurosurgeon is undertaken as soon as the infant is medically stable.
- If reconstruction is to be done in one stage:
    - Complete penile disassembly and division of the intersymphyseal band are crucial steps to allow for posterior positioning of the bladder and urethra.
- Then reconstruction of the bladder, penis, abdomen, and pelvis approximates the normal anatomy.
- Osteotomies are almost always necessary to assist in closure and posterior placement of the lower urinary tract. This allows a tension-free approximation of the widely separated pubic bones and of the anterior abdominal wall. In cases of extreme pubic diastasis, combined anterior innominate and posterior osteotomy can be done or osteotomy is performed along with external fixator placement for 2–3 weeks.
- Postoperative drainage and immobilization are important via ureteral stents, a suprapubic catheter and possibly a urethral catheter along with traction and casting similar to that in classic bladder exstrophy.
- In males with cloacal exstrophy, the penis is usually represented by two widely separated small phallic structures. Reconstruction of these is difficult and challenging.
    - Epispadias repair can be performed at the same time of initial closure when adequate corporal tissue is present.
    - Repair of epispadias can also be delayed.
    - In those with very small and insufficient phallic tissue, a female sex rearing should be considered and discussed with the

  family. This however should be considered only in severe cases.
  - In females, the hemi clitoris are brought together and duplicate vaginas are joined in the midline if possible.
  - In the genotypic male patient raised as a female, new vagina construction is usually delayed till the time of puberty.
- Abdominal Wall and Bladder Closure
  - Bilateral iliac osteotomies enable closure of the urinary bladder, abdominal wall and the widely separated pubic rami.
  - Urinary bladder closure, omphalocele closure and intestinal diversion are performed with pelvic osteotomies within the first 48–72 h of life.
  - A two-staged approach is indicated in those with other associated anomalies, widely separated pubic bones, a small bladder template or if the patient is not medically fit. The omphalocele is repaired together with intestinal diversion. At about 6 months later, the patient undergoes osteotomy and then, bladder closure and genital revision.
- Postclosure Management:
  - The patients are kept immobilized postoperatively for 4–6 weeks to allow the osteotomies to heal.
  - A modified Cantwell-Ransley repair of epispadias is planned at around 1 year of age.
  - Following epispadias repair, the patient's bladder capacity is measured annually with gravity cystogram.
  - The majority of cloacal exstrophy patients require an augmentation cystoplasty and continent catheterizable stoma or a continent urinary diversion. This is done at 6–8 years of age.
  - During this procedure the patient will either undergo a Young-Dees-Leadbetter bladder neck reconstruction or bladder neck transection along with ureteral reimplantation to prevent further vesicoureteral reflux.
  - Male patients, who continue to be raised as males, may require a phalloplasty or neophallus if their original phallus is very small.

13.5.9 Management of Urinary Incontinence

- Incontinence of urine is common in patients with cloacal exstrophy.
- This may be due in part to spinal defects, which can cause a neurologic deficit in bladder function, or to a small bladder capacity, which may require augmentation.
- Intermittent catheterization is important to enhance bladder outlet resistance.
- Urinary continence is possible in most children with cloacal exstrophy but usually will require a bladder augmentation and intermittent catheterization.
- Surgery to produce a continent reservoir should be delayed until the child is old enough to participate in self-care.
- The choice between a catheterizable urethra or an abdominal stoma depends on the adequacy of the urethra and bladder outlet, the intellect and dexterity of the child, and the child's orthopedic status as regards to the spine, hip joints, braces and ambulation.
- Bladder augmentation should be delayed until bowel function is mature and nutrition and acidosis are no longer a problem.
- Bladder augmentation can be done using hindgut or ileum but to avoid further loss of bowel, part of the stomach can be used as a gastrocystoplasty.
- There is a small risk of long-term cancer with gastrocystoplasty.

13.5.10 Prognosis

- In bladder exstrophy and cloacal exstrophy, the single most important predictor of long-term bladder growth and continence is successful primary bladder closure.
- The postoperative continence in patients with bladder exstrophy and cloacal exstrophy ranges from 70 % to 80 %.

13.5.11 Complications

- The most common complications of both Cantwell-Ransley and complete penile disassembly epispadias repair are persistent chordee, urethrocutaneous fistula, and wound dehiscence.
- A complication specific to the Mitchell repair's complete disassembly technique is glans and/or corporeal ischemia.
- Complications following repair of bladder exstrophy and cloacal exstrophy include:
  - Wound dehiscence
  - Bladder prolapse
  - Bladder outlet obstruction
  - Vesicocutaneous fistula
- Complete primary repair of exstrophy may be complicated by penile loss following penile disassembly.
- Intestinal complications following repair of cloacal exstrophy include;
  - Ileus
  - Volvulus
  - Small bowel obstruction
- Augmentation cystoplasty and continent urinary diversion may be complicated by:
  - Bladder calculi
  - Chronic bacterial colonization
  - Epithelial polyps
  - Mucus overproduction
  - Augmentation cystoplasty may be complicated by metabolic acidosis and carcinoma
  - The creation of stoma may be complicated by stenosis, prolapse, ischemia, and leakage

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14 Megacystis Microcolon Intestinal Hypoperistalsis Syndrome (Berdon Syndrome)

14.1 Introduction

- Berdon syndrome, also called Megacystis-microcolon-intestinal hypoperistalsis syndrome (MMIH syndrome), is an autosomal recessive fatal genetic disorder affecting newborns.
- It is a familial disturbance of unknown etiology.
- It was first described by Walter Berdon et al. in 1976.
- They described the condition in five female infants, two of whom were sisters. All had marked dilatation of the bladder and some had hydronephrosis and the external appearance of prune belly. The infants also had microcolon and dilated small intestines (Fig. 14.1).
- Megacystis microcolon intestinal hypoperistalsis syndrome (MMIHS) is the most severe form of functional intestinal obstruction in the newborn.
- The etiology of MMIHS is unknown.
- Megacystis Microcolon Intestinal Hypoperistalsis Syndrom (MMIHS) is found in females three or four times more than in males.
- It is characterized by (Figs. 14.2, 14.3, 14.4, 14.5, and 14.6):
  - A dilated, giant non obstructed urinary bladder (megacystis)
  - Urinary retention
  - Microcolon
  - Hypoperistalsis or absent peristalsis of the gastrointestinal tract leading to functional intestinal obstruction.
  - Hydronephrosis
  - Dilated small bowel
  - The pathological findings consist of an abundance of ganglion cells in both dilated and narrow areas of the intestine.
- MMIHS carries a poor prognosis and most of the cases die within the early months of their lives, nevertheless there are some case reports recently of long-term survival.
- These cases mostly die from malnutrition, sepsis, kidney failure, and liver failure depending on TPN and the complications of TPN.
- In 2011 and in an extensive review of 227 children with the MMIHS, Gosemann and Puri reported a 19.7 % survival rate and the oldest reported survivor was 24 years old. The vast majority of the surviving patients had to be maintained by total or partial parenteral nutrition (TPN). The main causes of death were sepsis, malnutrition and multiple organ failure.
- Prenatal diagnosis of MMIHS is possible by antenatal ultrasound and an antenatal ultrasound finding of an enlarged urinary bladder and intraabdominal mass in a female fetus should alert the treating physicians for MMIHS.
- The usual presentation of newborns with MMIHS is abdominal distension. This is caused by a markedly distended, but non-obstructed urinary bladder. This usually fills the whole abdomen and may reach to the xiphisternum.

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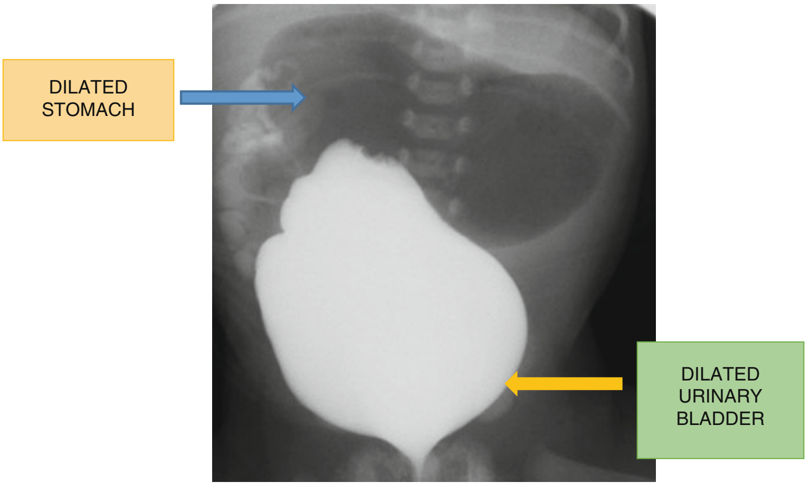
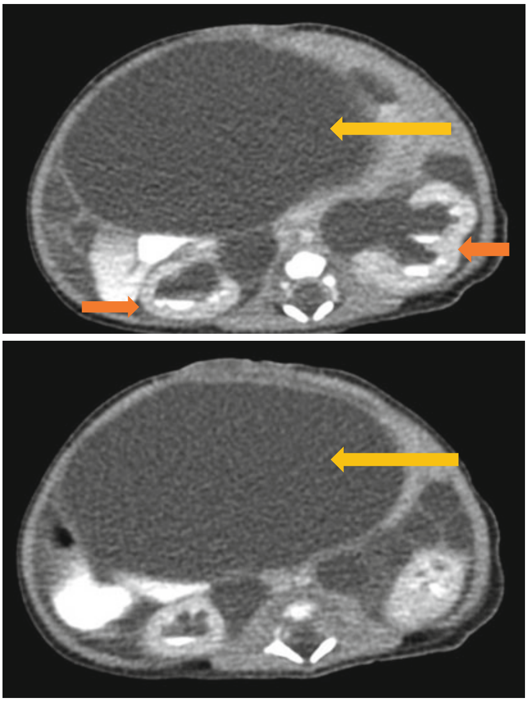
A.H. Al-Salem, *An Illustrated Guide to Pediatric Urology*, DOI 10.1007/978-3-319-44182-5_14

Fig. 14.1 A micturating cystourethrogram showing a markedly enlarged urinary bladder. Note also the dilated stomach. There was no evidence of vesicoureteral reflux





Figs. 14.2 and 14.3 Abdominal CT-scans showing a markedly dilated urinary bladder. Note also the associated bilateral hydronephrosis

- Treatment is supportive and involves an ileostomy to defunction the colon, with TPN.
- Multiorgan transplantation is suggested as a valuable alternative for children with severe gastrointestinal dismotility.

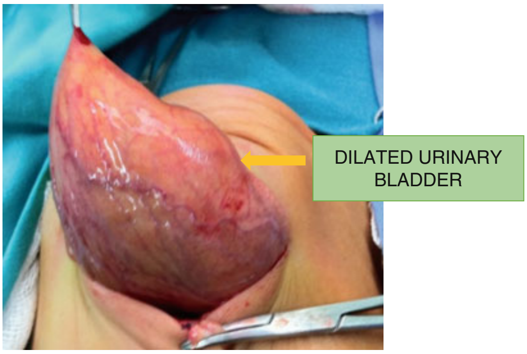
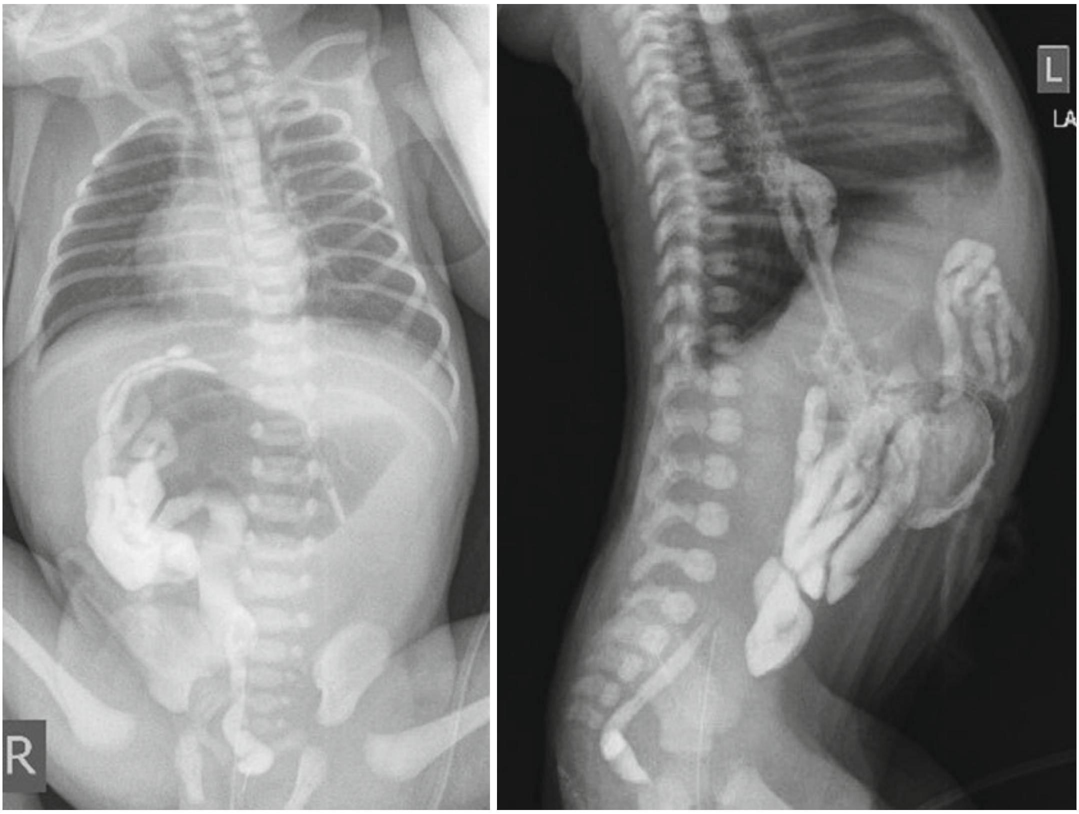


Fig. 14.4 An intraoperative clinical photograph showing a markedly dilated urinary balder. Note the thick wall of the enlarged urinary bladder

14.2 Etiology

- MMIHS is a rare congenital anomaly inherited as an autosomal recessive and predominantly affects females (4:1 ratio).
- There are however reports of sporadic cases.
- MMIHS is inherited as an autosomal recessive with the gene locus at 15q11.
- The exact etiology of MMIHS is not known.
- There are several theories to explain its pathogenesis but the most commonly accepted etiology is that MMIHS is a form of visceral myopathy.
- This was supported by histological studies which showed smooth muscle myopathy as



Figs. 14.5 and 14.6 Lower contrast enema showing small unused microcolon

the most predominant intestinal manifestation. This affects both the circular and longitudinal layers of the small bowel muscularis propria.

- Histological studies of the myenteric and submucosal plexuses of the bowel of MMIHS patients have found normal ganglion cells in the majority of the patients, decreased in some, hyperganglionosis and giant ganglia in others.
- An imbalance in intestinal peptides was suggested as one of the possible causes of hypoperistalsis.
- Absence of Interstitial Cell of Cajal (Pacemaker cells) in the bowel and urinary bladder has been reported as a causative factor.
- Puri and coworkers showed vacuolar degenerative changes in the smooth muscle cells with abundant connective tissue between muscle cells in the bowel and bladder.
- Several subsequent reports have confirmed evidence of intestinal myopathy in MMIHS.
- MMIHS has been reported with excessive smooth muscle glycogen storage postulating the pathogenesis involving a defect of glycogen-energy utilization.
- Other investigators have reported absence or marked reduction in smooth muscle actin and other contractile and cytoskeletal proteins in the smooth muscle layers of bowel in MMIHS
- Molecular analysis have linked the disease to the neuronal nicotinic acetylcholine receptor (ηAChR), namely the absence of a functional α3 subunit of the ηAChR, a de novo deletion of the proximal long arm of chromosome 15 (15q11.2).
- Immunohistochemical staining for smooth muscle actin, however, was selectively absent in the circular layer, demonstrating isolated absence in a unique and previously undescribed pattern. These observations raise the

possibility that the proximal long arm of chromosome 15 (15q11) may be of clinical significance in MMIHS.

- Histological evaluation of biopsies showed normal or excessive amounts of ganglion cells both in the dilated and collapsed parts of intestines. In some reports, the ganglion were present but described as mostly immature.
- In addition, there was vacuolization and degeneration in bladder and intestinal smooth muscles.

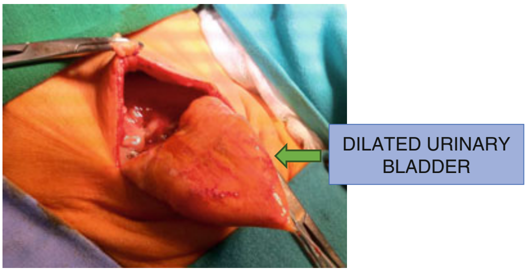


Fig. 14.7 A clinical intraoperative photograph showing a markedly dilated urinary bladder

14.3 Clinical Features

- Polyhydramnios is present in about 25 % of MMIHS cases.
- The main manifestation of MMIHS is abdominal distension secondary to the dilated non-obstructed urinary bladder (Fig. 14.7).
- Usually, infants present with bilious vomiting and abdominal distension caused by functional intestinal obstruction and bladder distension.
- Failure to pass meconium and features of intestinal obstruction.
- MMIHS is characterized by the presence of:
  - A markedly distended urinary bladder without distal urinary tract obstruction. This is palpable clinically and if a urinary catheter is passed, a large amount of urine will be drained and the size of the distended urinary bladder will decrease. It is important not to empty the distended urinary bladder rapidly.
  - Small unused microcolon. There is failure to pass meconium and a naso-gastric tube will drain bile stained fluid due to upper intestinal obstruction.
  - Decreased or absent intestinal peristalsis.

14.4 Associated Anomalies

- Megacystis Microcolon Intestinal Hypoperistalsis Syndrome is characterized by:
  - A dilated non-obstructed urinary bladder. This is associated with bilateral hydroureters and hydronephrosis.
  - Microcolon.
  - Dilated stomach and proximal small bowel (Figs. 14.8, 14.9, and 14.10).
  - Dilated esophagus.
- Other reported associated anomalies include:
  - Intestinal malrotation
  - Short bowel
  - Segmental stenosis of small intestine
  - Bilateral streak gonad
  - Bilateral duplicated urinary system
  - Omphalocele
  - Meconium ileus (Figs. 14.11 and 14.12)

14.5 Diagnosis

- Prenatal diagnosis of MMIHS is possible by antenatal ultrasound.
- This usually shows an intra-abdominal mass representing the enlarged urinary bladder and bilateral hydroureters and hydronephrosis.
- Plain abdominal x-ray will show a dilated stomach with little gas distally (Fig. 14.13).
- The diagnosis of MMIHS is confirmed by demonstrating a dilated non-obstructed urinary bladder and a small unused microcolon.
- This can be demonstrated by an abdominal ultrasound, abdominal CT-scan, a micturating cystourethrogram and a contrast enema (Fig. 14.14).
- The dilated stomach and esophagus can be outlined by an upper contrast study.

14.6 Treatment and Prognosis

- The management of MMIHS is supportive as there is no definite cure.
- The majority of patients with MMIHS die within the first year of life. These patients mostly die from:
  - Malnutrition
  - Sepsis
  - Renal failure
  - Liver failure
- Treatment is supportive and involves:
  - A central line should be inserted for long term total parenteral nutrition.
  - An ileostomy to decompress the small intestine (Figs. 14.15 and 14.16).
  - A urinary catheter or a vesicostomy to drain the dilated urinary bladder.
- A vesicostomy to decompress the distended urinary bladder is a better alternative for long-term drainage of the urinary bladder.
- MMIHS is known to have a high mortality but there are however reports of long term survivors.
- The survival in MMIHS in recent years has improved. The majority of survivors are either maintained by TPN or have undergone multi-organ transplantations.

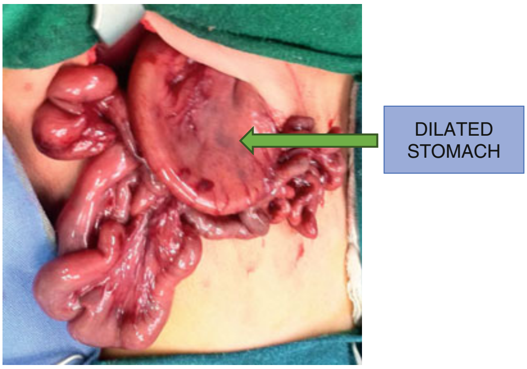
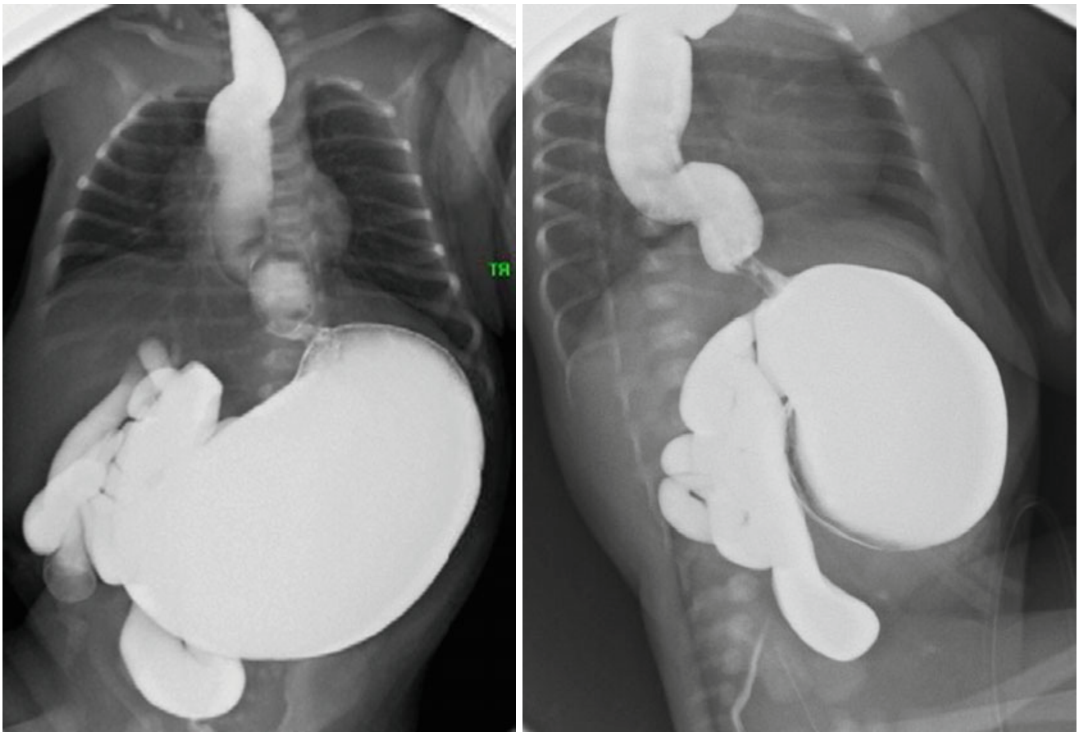
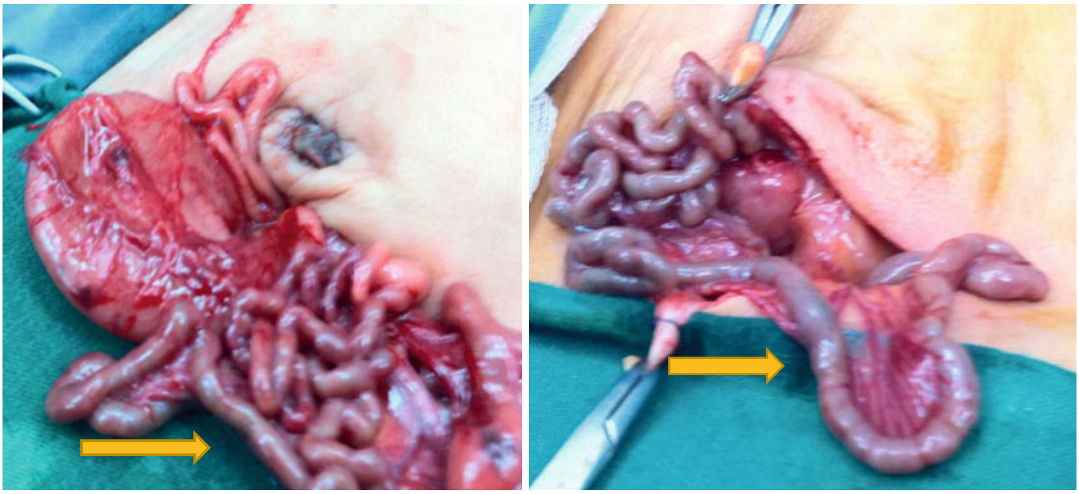


Fig. 14.8 Intraoperative photograph showing a markedly dilated stomach with a nasogastric tube in a patient with MMIHS



Figs. 14.9 and 14.10 Barium swallow and meal showing markedly dilated esophagus, stomach and upper part of the small intestines in a newborn with MMIHS



Figs. 14.11 and 14.12 Intraoperative photographs showing dilated stomach and small intestines filled with inspissated meconium (meconium ileus) in a patients with MMIHS

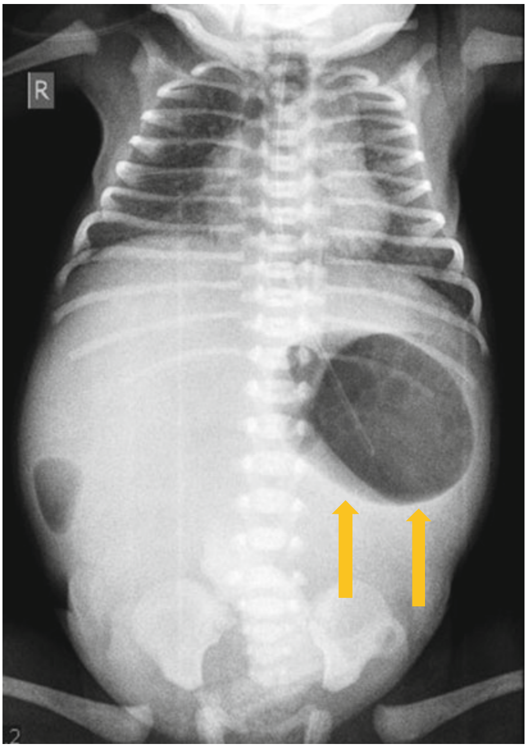


Fig. 14.13 Abdominal X-ray showing dilated stomach with little air distally

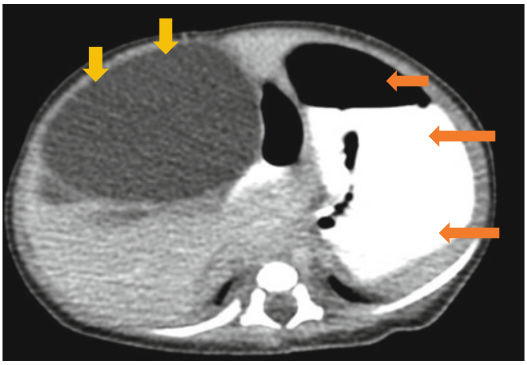
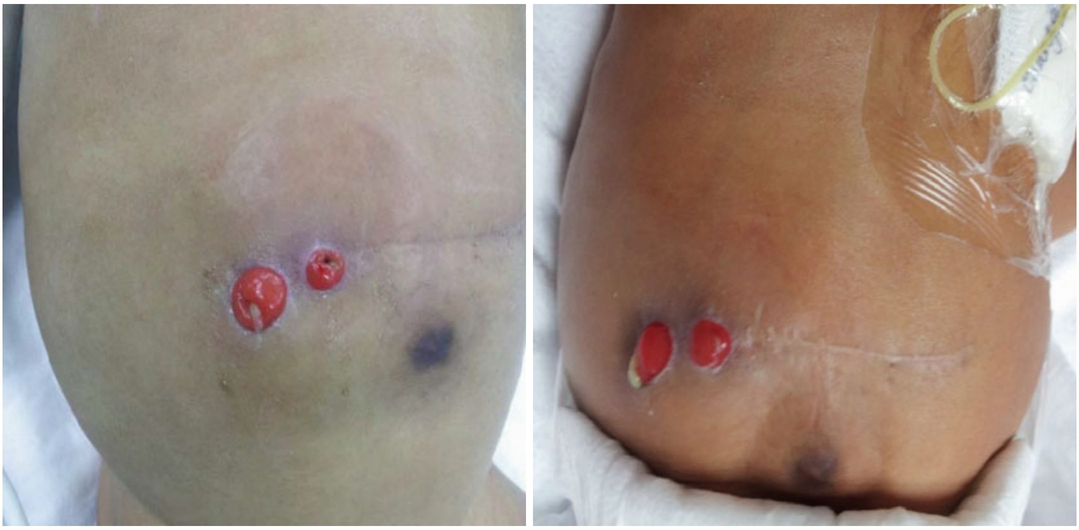


Fig. 14.14 Abdominal CT-scan with oral contrast showing a markedly dilated stomach. Note also the dilated urinary bladder

- Several attempts at multi-organ transplantation or combined liver and intestinal transplant in infants with MMIHS have been reported to be successful.
- Currently, multivisceral transplantation is the only accepted treatment modality for these patients.



Figs. 14.15 and 14.16 Clinical photographs showing the two stomas (ileostomies) in patients with MMIHS. The proximal stoma never functioned. Note also the central line inserted for total parenteral nutrition

Further Reading

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Cloacal Anomalies

15

15.1 Introduction

- In animal anatomy, a cloaca/kloʊˈeɪkə/*kloh*-*ay*-*kə* (plural cloacae /kloʊˈeɪsiː/*kloh*-*ay*-*see*) is the posterior orifice that serves as the only opening for the digestive, reproductive, and urinary tracts of certain animals.
- All amphibians, birds, reptiles, and a few mammals have this orifice, from which they excrete both urine and feces.
- This is in contrast to most placental mammals, which have two or three separate orifices for evacuation.
- The word cloaca comes from Latin, and means sewer derived from *cluō*, which meant "cleanse".
- A persistent cloaca is a complex congenital birth defect in which there is a confluence of the rectum, vagina, and urethra into a single common channel (Figs. 15.1 and 15.2).
- The exact incidence of cloacal anomalies is unknown but it is estimated to occur in 1 per 20,000–25,000 live births.
- Cloacal anomalies occur exclusively in girls.
- They comprise the most complex defect in the spectrum of anorectal malformations.
- The management of these patient is challenging and these patients should be managed in specialized centers with surgeons experienced in the management of these patients.
- The goals of treatment include an anatomic reconstruction with the aim of achieving:
  - Urinary control
  - Bowel control
  - Sexual function
- Persistent cloacae occur exclusively in girls and is considered the most complex and technically challenging defect in the spectrum of anorectal malformations.
- The etiology of persistent cloaca is unknown.
- A common error in the diagnosis of cloaca may occur during the neonatal period where physician may confuse it with high anorectal malformation with a rectovaginal fistula.
- The cooperation of a pediatric surgeon and pediatric urologist is important in this regard.
- Cloacae represent a spectrum of defects, but the common denominator is the presence of a single perineal orifice and the rectum, vagina, and urethra open into a single common channel.
- The length of this common channel is variable and ranges from 1 to 10 cm, with an average length of approximately 3 cm.
- The length of this common channel is important both surgically and also for prognosis.
- More than 80 % of all patients with a cloaca have an associated urogenital anomaly.
- All patients must be evaluated at birth for an associated urologic malformation.

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A.H. Al-Salem, *An Illustrated Guide to Pediatric Urology*, DOI 10.1007/978-3-319-44182-5_15

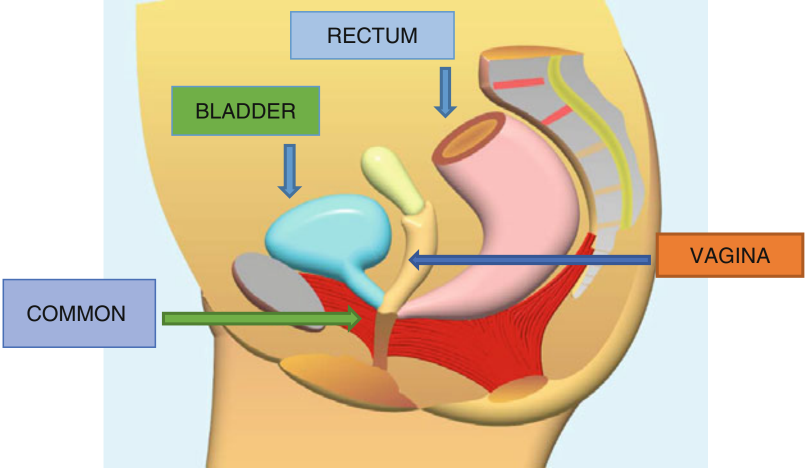


Fig. 15.1 A diagrammatic representation of cloaca. Not the urethra, vagina and rectum opening in a common channel. The length of the common channel is important for prognosis

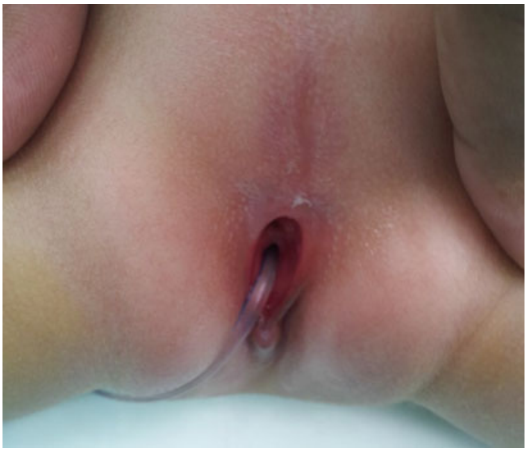


Fig. 15.2 A clinical photograph of a patient with cloaca. Note the common single perineal opening. No separate urethral or anal openings seen

- The goals of treatment include an anatomic reconstruction to achieve bowel and urinary control, as well as normal sexual function.
- In 1982, Pena introduced the posterior sagittal approach to repair high anorectal malformation. This technique was also used to repair cloacal malformations.
- This technique is extended and used to repair the more complex cloacae and it is called the posterior sagittal anorectovaginourethroplasty (PSARVUP).
- This approach allowed for direct exposure to the complex anatomy and an excellent visualization and repair of the voluntary muscles of urinary and fecal continence.
- It is important to accurately diagnose persistent cloaca in the neonatal period because 90 % of these patients have an associated urologic problem, and 40 % of them may present also with an abdominal mass secondary to hydrocolpos.
- The hydrocolpos may produce two important complications:
  - It may compress the trigone of the urinary bladder, producing ureterovesical obstruction, megaureter, and hydronephrosis.
  - The vagina may become obstructed leading to accumulation of the cervical glands secretion. This leads to the formation of hydrocolpos.
  - Hydrocolpos if left undrained may become infected, leading to a pyocolpos.
- Approximately 40 % of patients with cloaca have a double Mullerian system consisting of two hemiuteri and two hemivaginas.
- This septation disorder may be partial or total and symmetric or asymmetric.
- It is important to recognize and document this for future follow-up of these patients.
- The urinary tract and the distended vagina (Hydrocolpos) may both need to be managed within the newborn period to avoid serious complications. Drainage of the distended vagina may lead to resolution of the secondary urological complications.

- The goals of management of cloaca include:
  - Early and accurate diagnosis of both cloaca and associated anomalies.
  - Immediate neonatal management including fecal, urinary and vaginal diversion depending on the presentation.
  - An anatomic reconstruction to achieve bowel and urinary control, as well as normal sexual function.
- Currently, the posterior sagittal anorectovaginourethroplasty (PSARVUP) is the preferable approach to treat cloacal malformations. This approach is important for direct exposure to the complex anatomy and also allows excellent visualization of the voluntary muscles of urinary and fecal continence.

15.2 Associated Anomalies

- Associated anomalies are common in patients with cloaca.
- More than 80 % of all patients with a cloaca have an associated urogenital anomaly.
- These include:
  - Absent kidney
  - Vesicoureteral reflux
  - Horseshoe kidney
  - Ectopic ureters
  - Double ureters
  - Hydronephrosis, and megaureters as a result of vesicoureteral reflux or ureterovesical obstruction.
- Tethered cord:
  - Tethered cord has a known association with anorectal malformations and is particularly common in patients with persistent cloaca.
  - A tethered spinal cord refers to an intravertebral fixation of the phylum terminale.
  - This may result in motor and sensory disturbances of the lower extremities.
  - Spinal ultrasonography in the first 3 months of life and MRI thereafter are useful in diagnosis of tethered cord and associated spinal and sacral anomalies.
  - Patients with tethered cord have a worse functional prognosis regarding bowel and urinary function.
  - Add to this the less-developed sacra, associated spinal problems, and less-developed perineal musculature.
  - The input of a neurosurgeon in this is important as release of a tethered cord may improve the functional outcome especially the urodynamics.
  - Anomalies of the sacrum, particularly hypodevelopment, sacral hemivertebrae, and hemisacra, are associated with tethered cord and most likely comprise the spectrum of caudal regression, of which spinal anomalies are a part.
- Patients with anorectal malformations and tethered cord have a worse functional prognosis regarding bowel and urinary function.
- Sacrum and spine anomalies:
  - The sacrum is the most frequently affected bony structure.
  - Associated anomalies of the sacrum include hemisacrum, hypodevelopment of the sacrum and sacral hemivertebrae.
  - The degree of sacral deficiency is assessed by calculating the sacral ratio.
  - The sacrum is measured, and its length is compared with bony parameters of the pelvis on an anteroposterior and a lateral radiographs.
  - Calculation of sacral ratio:
    - The distance from the coccyx to the sacroiliac joint divided by the distance from the sacroiliac joint to the top of the pelvis.
  - The assessment of the hypodevelopment of the sacrum correlates with the patient's functional prognosis.
  - Normal sacra have a ratio of greater than 0.7.
  - Bowel control has rarely been observed in patients with ratios less than 0.3.
  - A hemisacrum is almost always associated with a presacral mass, commonly a presacral teratoma, or an anterior meningocele.
  - This may be part of the Currarino triad, which includes:
    - An anorectal malformation
    - A hemisacrum
    - A presacral mass

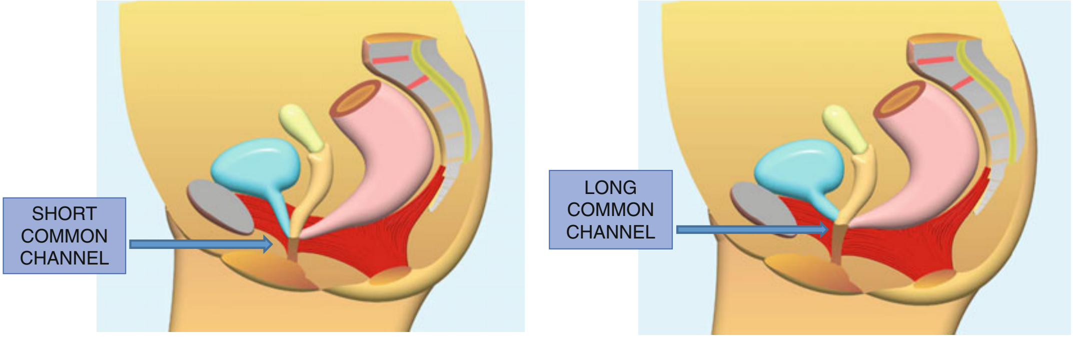
  - Hemivertebrae may also affect the lumbar and thoracic spine, leading to scoliosis.
  - Patients with cloaca may also have spinal anomalies other than tethered cord, such as syringomyelia and myelomeningocele.
- Genital anomalies:
- Approximately 50 % of patients have various degrees of vaginal or uterine septation.
  - Absent vagina
  - 2 hemivagina
  - 2 hemiuteri

15.3 Classification

- Cloacae represent a wide spectrum of anomalies.
- In all, the rectum, vagina and urethra open together in a common channel.
- The length of this common channel is variable and ranges from 1 to 10 cm with an average of 3 cm.
- The length of this common channel is important both for management and prognosis.
- Based on the length of the common channel cloacae are divided into two main groups:
  1. Short common channel: The length of the common channel is less than 3 cm (Figs. 15.3 and 15.4)
  2. Long common channel: The length of the common channel is more than 3 cm (Fig. 15.4).

15.4 Clinical Features

- Persistent cloaca is a clinical diagnosis that is usually made in the neonatal period.
- The diagnosis of persistent cloaca is made clinically (Fig. 15.5).
- Normally, there are three perineal openings, a urethral opening, a vaginal opening and an anal opening.
- The presence of only two openings (a urethra and vaginal openings) suggests an anorectal malformation.
- The presence of a single perineal orifice is diagnostic clinically of a persistent cloaca.
- The presence of abdominal distension with a palpable abdominal mass is most likely secondary to a distended vagina (hydrocolpos) (Figs. 15.6 and 15.7).
- A hydrocolpos is present in 40 % of patients with persistent cloaca.
  - The distended vagina is a common cause of an obstructed urinary tract because of its pressure on the trigone.
  - These patients may initially have hydronephrosis and hydroureter and once the vagina is decompressed, the urinary tract may no longer be obstructed.
  - If the hydrocolpos is not drained during the newborn period, it can become infected (pyocolpos) and can lead to sepsis and vaginal scarring.



Figs. 15.3 and 15.4 Diagrammatic representation of cloaca. Note the length of the common channel which is variable ranging from 1 to 10 cm but commonly around 3 cm. The cloaca is divided into two types, low and high based on the length of the common channel. It is a short common channel if the length of the common channel is less than 3 cm and log common channel if it is more than 3 cm

- The external genitalia in these patients are usually not well developed and often appear small.
- Some of these patients may present with abdominal distension and examination of the abdomen may reveal an abdominal mass, which likely represents a distended vagina (hydrocolpos) and is present in about 40 % of patients with persistent cloaca.
- The distended vagina may also lead to distension of the uterus leading to hydrometrocolpos and sometimes the fluids distending the uterus may spill over to the peritoneal cavity via the Fallopian tubes leading to ascites.
- The distended vagina is also a common cause of an obstructed urinary tract because of its pressure on the trigone of the urinary bladder.
- This leads to obstruction of the uretro-vesical junction leading to hydroureter and hydronephrosis.
- A severe hydronephrosis may lead to calyceal rupture with urine extravasation either retroperitoneally or in the peritoneal cavity.
- It is important to decompress the distended vagina as soon as possible and once the vagina is decompressed, the urinary tract may no longer be obstructed and usually the hydroureter and hydronephrois resolve.
- If the hydrocolpos is not drained during the newborn period, it can become infected leading to pyocolpos. This is a serious condition which may lead to septicemia.
- A hemisacrum in these patients is almost always associated with a presacral mass, commonly teratomas, or anterior meningoceles.
- The Currarino triad includes:
  - An anorectal malformation
  - A hemisacrum
  - A presacral mass (teratoma, anterior meningocele)

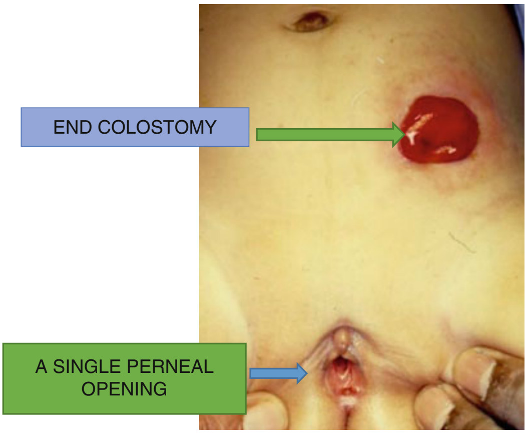
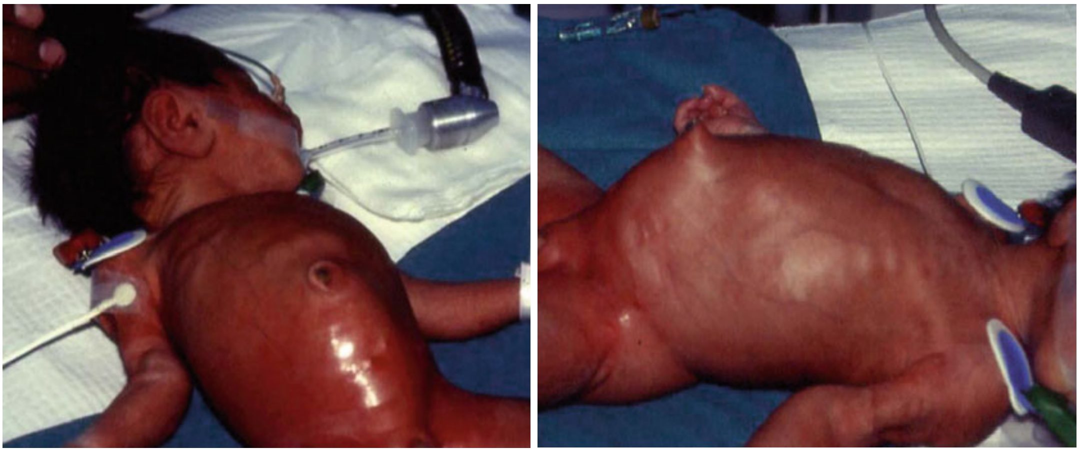


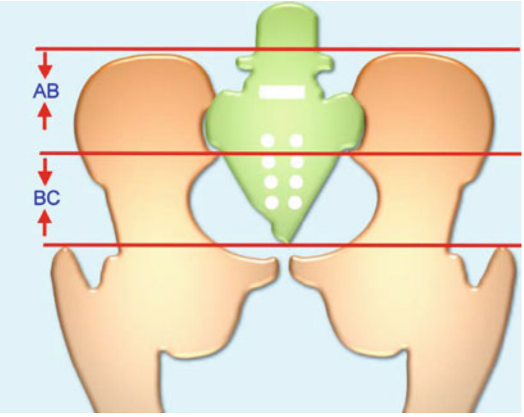
Fig. 15.5 A clinical photograph showing a not well developed external genitalia in a patient with cloaca. Not also the colostomy which was done in the newborn period. Note also the presence of a single perineal opening



Figs. 15.6 and 15.7 Clinical photographs of a newborn with cloaca showing abdominal distension secondary to hydrocolpos

15.5 Investigations

- Plain radiography of the spine:
  - This is to look for spinal anomalies, such as spina bifida and spinal hemivertebrae.
- Plain radiography of the sacrum:
  - This is to look for sacral anomalies, such as a hemisacrum and sacral hemivertebrae.
  - The degree of sacral hypodevelopment can also be assessed.
  - Traditionally, to evaluate the degree of sacral hypodevelopment, the number of sacral vertebral bodies was counted.
  - A more objective assessment of the sacrum can be obtained by calculating the sacral ratio.
  - To calculate the sacral ratio (Fig. 15.8):
    - The distance from the coccyx to the sacroiliac joint is measured and divided by the distance from the sacroiliac joint to the top of the pelvis.
    - To calculate the sacral ratio, a lateral radiography is more accurate than the anteroposterior view.
    - The sacral ratio is important as this correlates with the patient's functional prognosis.
    - The normal sacral ratio is greater than 0.7.
    - Bowel control has rarely been observed in patients with ratios less than 0.3.
  - A hemisacrum is almost always associated with a presacral mass, commonly a teratoma, or an anterior meningoceles.



NORMAL RATIO = BC ÷ AB = 0.74

Fig. 15.8 Diagrammatic representation of calculating the sacral ratio

  - The Currarino triad, which includes an anorectal malformation, a hemisacrum, and a presacral mass should be excluded.
- Abdominal ultrasonography is useful to evaluate intraabdominal organs including the vagina and uterus as well as the presence or absence of hydrocolpos.
- Spinal ultrasonography is also used in infants less than 3 month to evaluate for tethered cord.
- Echocardiography to detect associated cardiac anomalies.
- A distal loopogram in those with a preliminary colostomy. The position of the rectum must be carefully checked to determine whether it can be comfortably reached from a posterior sagittal incision (Fig. 15.9).
- Prior to definitive repair of cloacal malformations, it is important to determine the length of the common channel and the length of the urethra from the common channel to the bladder neck.
- This is determined using cystoscopy with vaginoscopy and a three-dimensional (3D) cloacagram under anesthesia. This is also valuable in studying the genital anatomy (vaginal septum, numbers and patency of cervices, and size and height of the vagina) (Fig. 15.10).
- A cloacagram is performed by injecting a water soluble contrast into the single perineal orifice and taking radiographs that will show the bladder, vagina and rectum and their anatomic relation. Cross-lateral radiographs are more informative as well as the length of the common channel.
- MRI is currently the procedure of choice to evaluate the anomalies of the cloaca, the presence of tethered cord, sacrum and spine. MRI is used in infants older than 3 months (Fig. 15.11).
- Cystoscopy and vaginoscopy are essential components for evaluation of the patient with persistent cloaca. These are usually performed before the main repair to define the anatomy and plan the surgical repair. The following anatomic points are checked:
  - The length of the common channel
  - The presence of a vagina
  - The presence of hemivagina

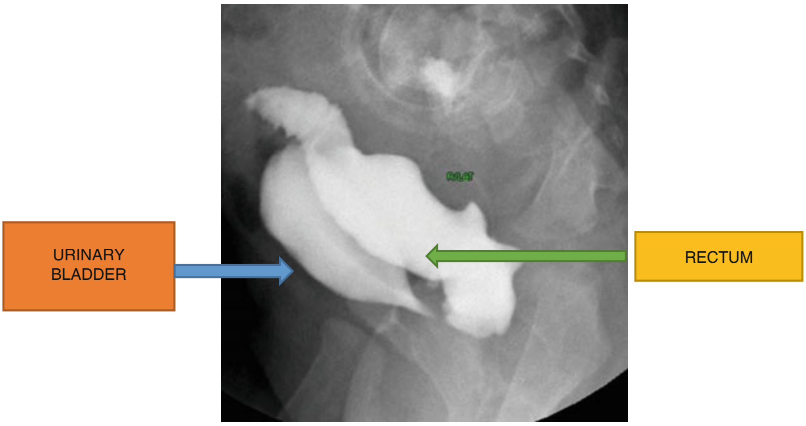


Fig. 15.9 A contrast study showing the urinary bladder and rectum in a patient with cloaca

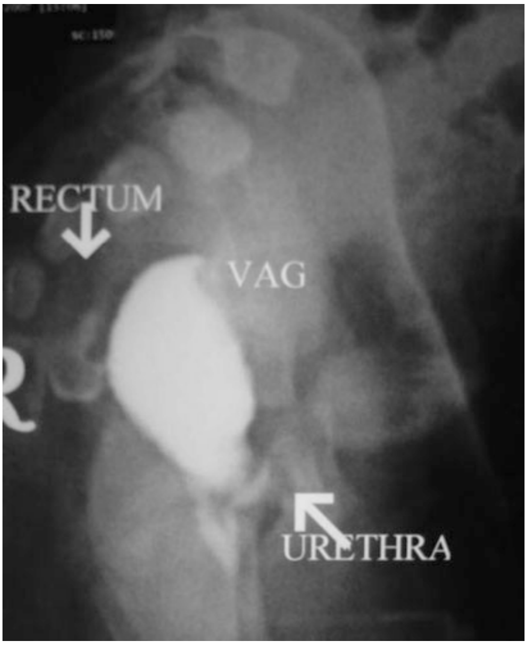


Fig. 15.10 A contrast study through the perineal opening showing the vagina, the urethral opening and rectum

  - The presence of a cervix (or cervices)
  - The visualization of the rectal fistula

15.6 Management (Figs. 15.12, 15.13, 15.14, 15.15, and 15.16)

- The goals of early management of cloaca are:
  - To detect associated anomalies.
  - To achieve satisfactory diversion of the gastrointestinal tract.
  - To drain associated hydrocolpos
  - To divert the urinary tract when necessary
  - To achieve bowel control, urinary control, and normal sexual function.
- Total diversion of the fecal stream is made with an end colostomy placed in the descending colon and with a mucous fistula.
- This total diversion of the fecal stream is important to prevent urinary infections.
- It is important to leave an adequate bowel length distal to the site of the colostomy for subsequent pull-through.
- The definitive procedure to repair cloaca is posterior sagittal anorectovaginourethroplasty.
- This procedure simultaneously repairs the rectal, vaginal, and urethral anomalies.
- The more complex anomalies are repaired using a combined abdominal approach and posterior sagittal anorectovaginourethroplasty.
- The repair of persistent cloaca represents a technical challenge and should be performed in specialized centers by pediatric surgeons dedicated to the care of these patients.
- The management of cloaca is performed in stages.
  - The first stage is in the newborn period and consists of fecal diversion and urinary and vaginal diversion if necessary.
  - The definitive repair of cloaca is performed at a later date. This is done using the posterior sagittal anorectovaginourethroplasty (PSARVUP). Complex cases will require laparotomy also. This depends on the

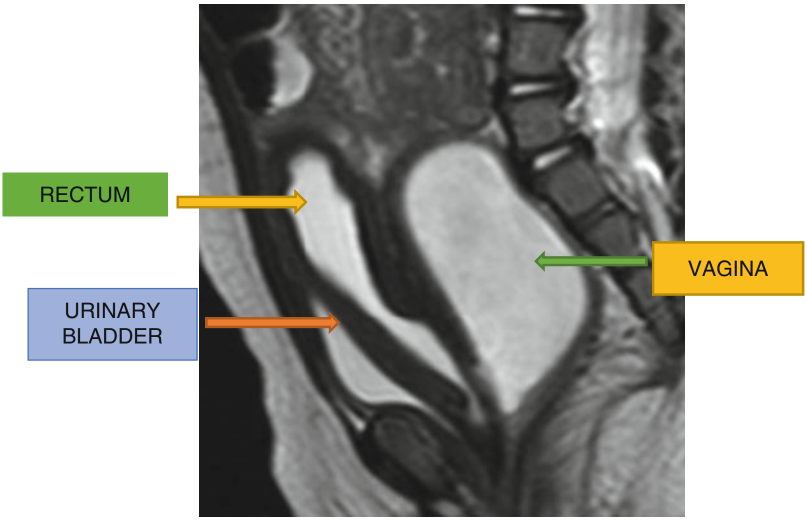


Fig. 15.11 MRI of a patient with cloaca showing the rectum, urethra and vagina joining distally together in a common channel

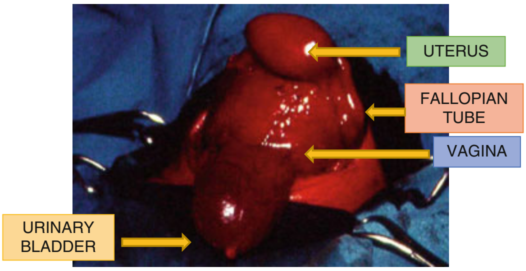
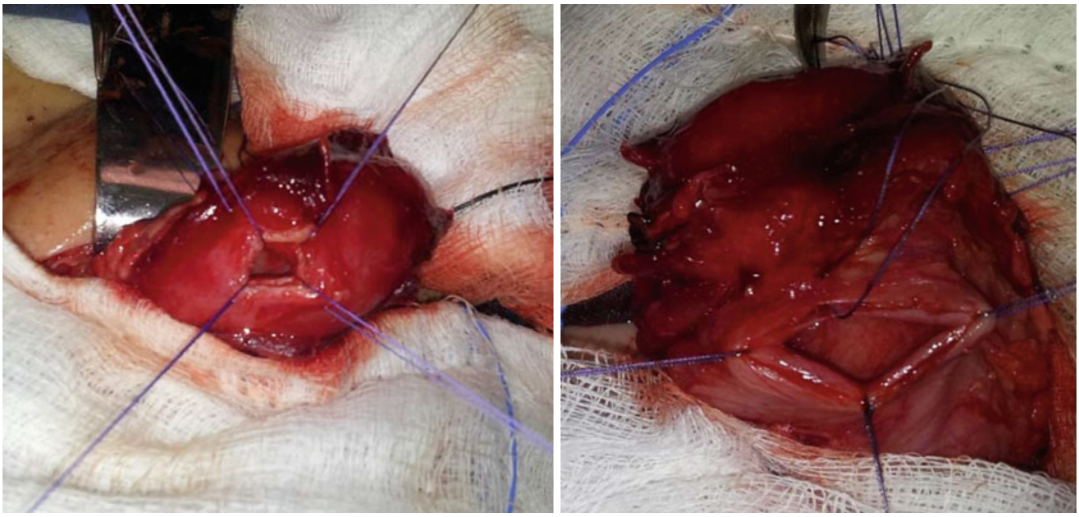
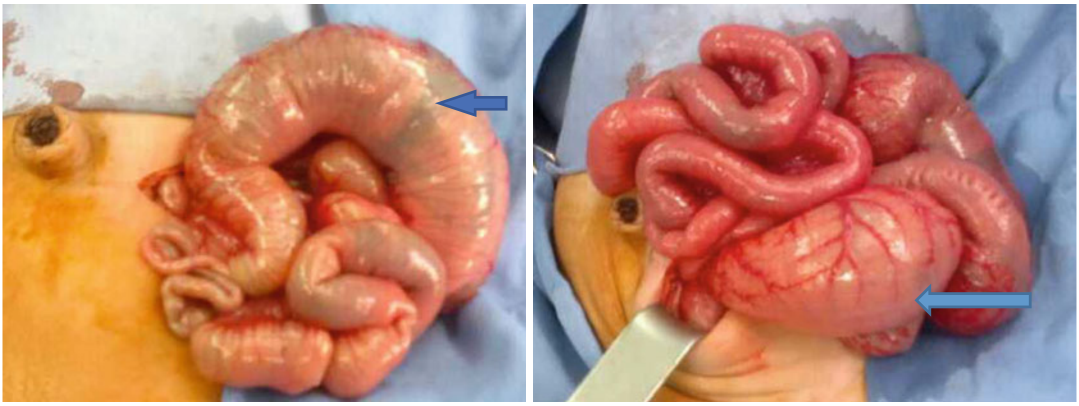


Fig. 15.12 An intraoperative photograph of a patient with cloaca who presented with hydrometrocolpos. Note the distended vagina and uterus

length of the common channel which varies from 1 to 10 cm.
  - This is followed by colostomy closure.
- The goals of surgical treatment are to achieve bowel control, urinary control, and normal sexual function. This depends on:
  - The quality of the sacrum and spine
  - The quality of the sphincter muscles
  - The length of the common channel
- If the common channel is shorter than 3 cm, the posterior sagittal approach can be used to repair the defect without an abdominal approach.
  - The rectum is mobilized first and the vagina and urethra are then mobilized together (total urogenital mobilization).
  - Total urogenital mobilization allows mobilization of the urethra and vagina as one structure.
- For patients with a common channel longer than 3 cm, a laparotomy is usually required.
  - The vagina and urinary tract are separated to gain length
  - The urethra is then reconstructed.
  - Complex vaginal mobilizations are often required, and vaginal replacement (with colon or small intestine) is frequently necessary
- Posterior sagittal anorectovaginourethroplasty (PSARVUP) consists mainly of:
  - Separating the rectum from the urogenital tract.
  - Followed by separation of the vagina from the urethra and bladder.
  - Reconstruction of the common channel as a neo-urethra.
  - Mobilization and dissection of the vagina so that it could be pulled down to be placed posterior to the urethra wall.
  - Performance of a pull-through of the rectum. The pull-through rectum is placed within the limits of the sphincter mechanism, which is determined with an electrical stimulator.
- The repair can usually be performed using only the posterior sagittal approach.
- For more complex anomalies, an abdominal approach is added to mobilize a very high vagina or gain length on a very high rectum.
- If the common channel is shorter than 3 cm, the posterior sagittal approach can be used to



Figs. 15.13 and 15.14 Intraoperative photographs of a patient with cloaca showing the already opened vagina which was distended secondary to hydrocolpos



Figs. 15.15 and 15.16 Intraoperative photograph showing dilated sigmoid colon in two patients with cloaca

repair the defect without an abdominal approach.

- For patients with a common channel longer than 3 cm, a laparotomy is usually required.
- Complex vaginal mobilizations are often required, and vaginal replacement (with colon or small intestine) is frequently necessary.
- Total urogenital mobilization is a technique that allows mobilization of the urethra and vagina as one structure.
- If total urogenital mobilization does not adequately lengthen the vagina, the vagina and urethra must be separated, which is a technically challenging procedure.
- The pulled-through rectum is placed within the limits of the sphincter mechanism, which is determined with an electrical stimulator.
- Total diversion of the gastrointestinal tract is achieved with a colostomy (a double barrel colostomy) placed in the descending colon. This leaves a sufficient length of the colon for subsequent pullthrough.
- Total diversion of the fecal stream is necessary to avoid spillage and prevent urinary tract infections.
- The patient must be left with a good length of distal colon long, enough for the future pullthrough, and sometimes for a vaginal replacement if needed.

- The mucous fistula is also important for radiologic evaluation of the distal colon.
- A Foley catheter is placed in the bladder and this remains in place for approximately 10–14 days. For more complex cases, a vesicostomy or suprapubic cystostomy tube may be needed for longer-term urinary diversion.
- Anal calibration is performed 2 weeks after the operation, followed by a program of anal dilatations.
- Once the desired size is reached, the colostomy can be closed.
- Cystoscopy and vaginoscopy should be performed before colostomy closure to ensure that no urethrovaginal fistula is present.
- A urethrovaginal fistula if present will need to be closed prior to colostomy closure.
- Patients with cloaca have no contraindications to definitive surgery when future fecal or urinary incontinence is a concern.
- Even for patients with incontinence, a bowel management program is almost always successful in keeping a patient clean and dry.
- In patients in whom bowel management is unsuccessful (<3 %), a permanent colostomy may be the best option to ensure good quality of life.
- In patients with urinary incontinence, many options are available for keeping a patient clean.
- Urinary diversions, such as the Mitrofanoff procedure and the use of intermittent catheterization, are usually successful in keeping the patient dry of urine.
- The repair of persistent cloaca represents a technical challenge and should be performed in specialized centers by pediatric surgeons dedicated to the care of these patients. This especially for cloaca with a long common channel.
- A distal colostogrphy through the mucous fistula is essential to outline the anatomy.
- Cystoscopy and vaginoscopy are essential components for better evaluation of the patient with persistent cloaca. This is important to define the anatomy and plan surgical reconstruction. It is important to determine the length of the common channel, the presence of vagina or a bifid vagina, the presence of one cervix or more and the site of rectal fistula. This is valuable and help the surgeon to predict whether a laparotomy will be required in combination with the posterior sagittal approach.
- Prognostic factors include:
  - The quality of the sacrum and spine.
  - The quality of the sphincter muscles.
  - The length of the common channel.
- Approximately 50 % of patients have various degrees of vaginal or uterine septation. These can be totally or partially repaired during the main operation.
- The Foley catheter remains in place for approximately 10–14 days.
- Anal calibration is performed 2 weeks after the operation, followed by a program of anal dilatations. Once the desired size is reached, the colostomy can be closed.
- Cystoscopy and vaginoscopy should be performed before colostomy closure to ensure that no urethrovaginal fistula is present, which would necessitate a reoperation which should be done with the colostomy still in place.
- Dilatations are continued afterward according to a prescribed protocol. They are a vital part of the postoperative management to avoid a stricture at the anoplasty site.
- Many of these patients require a bowel management program to keep them clean and dry.
- In patients in whom bowel management is unsuccessful (<3 %), a colostomy may be the best option to ensure good quality of life.
- In patients with urinary incontinence, many options are available for keeping a patient clean.
- Urinary diversions, such as the Mitrofanoff procedure and the use of intermittent catheterization, are usually successful in keeping the patient dry of urine.
- Many of these patients require prophylactic antibiotics for urinary tract infections for associated vesicoureteral reflux.
- Intermittent catheterization is required in 70 % of patients with persistent cloaca who have a common channel longer than 3 cm, compared

with 20 % in those with a common channel shorter than 3 cm.

- In most patients, the bladderneck is competent, and the patients who require catheterization remain dry between voids. If catheterization is not performed, overflow incontinence occurs.
- In those with non-competent bladderneck or nonexisting bladder neck, urinary diversion, such as a Mitrofanoff procedure, with bladder neck tightening may be needed.

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Urachal Remnants

16

16.1 Introduction

- The urachus is a fibrous remnant of the allantois.
- The allantois is a canal that drains the urinary bladder of the fetus and runs within the umbilical cord.
- The urachus is a band of fibrous tissue extending from the dome of the bladder to the umbilical cord.
- By 32 weeks, the urachus is obliterated and becomes a vestigial structure known as the median umbilical ligament (not to be confused with the medial umbilical ligament, which is a separate structure that lies laterally to the median umbilical ligament).
- The urachus remnant lies in the space of Retzius, between the transversalis fascia anteriorly and the peritoneum posteriorly.
- In 0.1–2.0 % of the population, the urachus remains patent and may result in urine leaking from the umbilicus or infected urachal cysts.
- Persistence of urachal remnant can give rise to various clinical problems:
  - Urachal cyst
  - Urachal fistula
  - Urachal diverticulum (Vesicourachal diverticulum)
  - Urachal sinus
- Because urachal remnants are uncommon and manifest with nonspecific abdominal or urinary signs and symptoms, definitive presurgical diagnosis is not easily made.
- The urachus is also known to undergo malignant transformation and adenocarcinoma is the commonest.
- A rare urachal tumor has been reported as a manifestation of IgG4-related disease.

16.2 Embryology

- Embryologically, the amniotic cavity bulges over the embryo and attaches to the yolk sac and the connecting stalk to form the umbilical cord.
- Further caudal folding of the embryo incorporates the proximal yolk sac into the hindgut and the allantois which is a diverticulum of the yolk sac into the urogenital sinus.
- The yolk and body stalks fuse to become the umbilical cord.
- In the third week of gestation, the allantois, which grows into the body stalk is formed as a diverticulum from the yolk sac.
- The allantois appears on about day 16 as a tiny, finger-like outpouching from the caudal wall of the yolk sac.
- The bladder develops from the ventral portion of the expanded terminal part of the hindgut, the cloaca, which is contiguous with the allantois ventrally.
- The cranioventral end of the bladder opens into the allantois at the level of the umbilicus; thus, the bladder initially extends all the way to the umbilicus.

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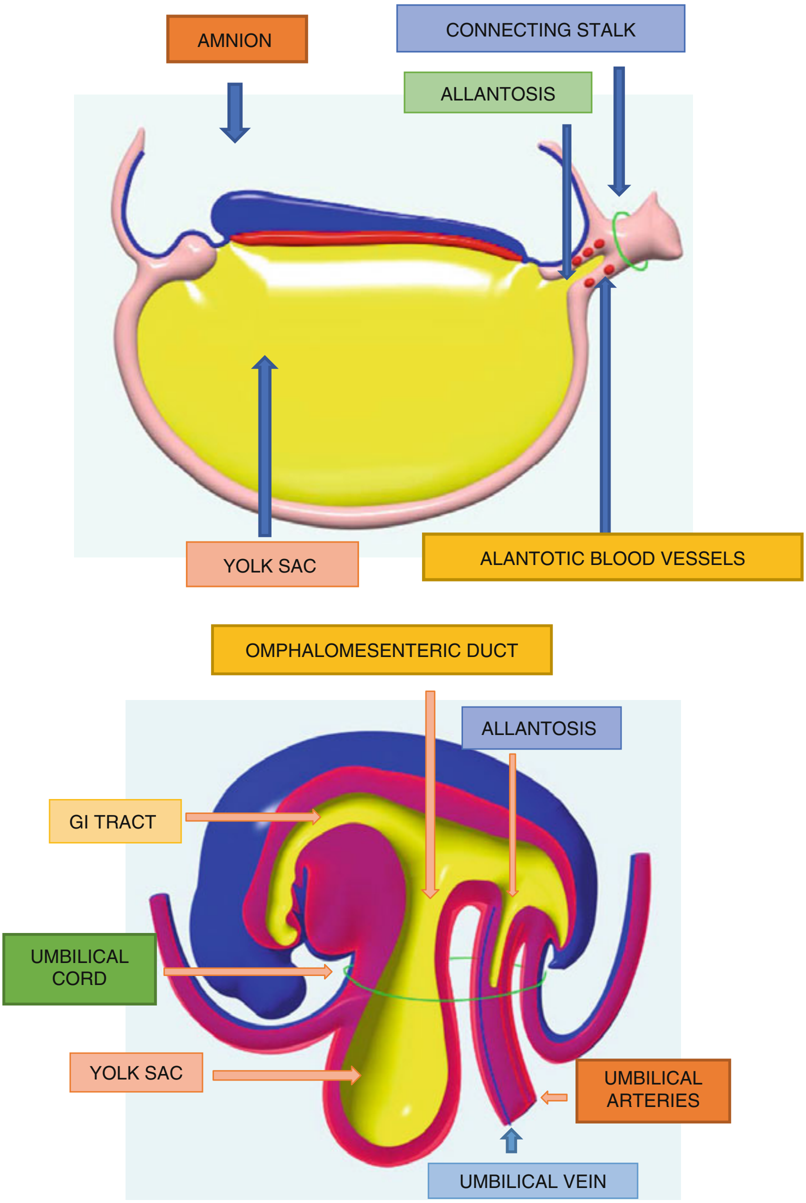
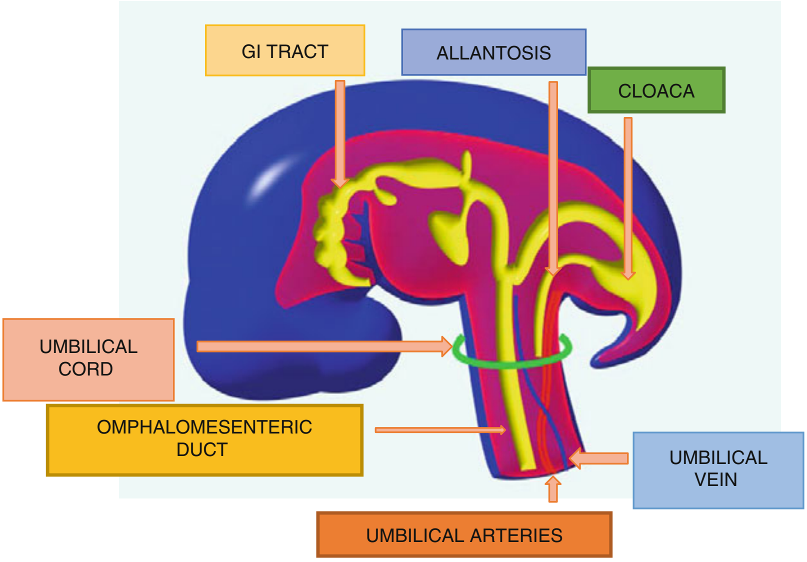
A.H. Al-Salem, *An Illustrated Guide to Pediatric Urology*, DOI 10.1007/978-3-319-44182-5_16

- By the fourth or fifth month of gestation, the bladder descends into the pelvis and its apical portion progressively narrows to a small, epithelialized fibromuscular strand, the urachus (Figs. 16.1, 16.2, and 16.3).
- In late embryonic and fetal life and early postnatal life, the urachal portion, which is still microscopic, fails to grow; thus, its lumen remains narrow and is usually obliterated by fibrous proliferation.
- In one-third of adults, it may be visible at microscopic examination as a structure communicating with the lumen of the bladder; however, in terms of function it can be considered closed by the latter half of fetal life.


AMNION
CONNECTING STALK
ALLANTOSIS
YOLK SAC
ALANTOTIC BLOOD VESSELS
OMPHALOMESENTERIC DUCT
ALLANTOSIS
GI TRACT
UMBILICAL CORD
YOLK SAC
UMBILICAL ARTERIES
UMBILICAL VEIN

Figs. 16.1, 16.2, and 16.3 Diagrammatic representations of the embryo at 3, 4 and 5 weeks of intra-uterine life. Note the developing allantosis and omphalomesenteric duct



Figs. 16.1, 16.2, and 16.3 (continued)

- The urachus varies from 3 to 10 cm in length and from 8 to 10 mm in diameter.
- It is a three-layered tubular structure, the innermost layer being lined with transitional epithelium in 70 % of cases and with columnar epithelium in 30 %.
- The structure is surrounded by connective tissue and an outermost muscular layer in continuity with the detrusor muscle.
- Occasionally, the urachus may merge with one or both of the obliterated umbilical arteries, and there may be a slight deviation to the right or left of the midline.
- As the distal hindgut and the urogenital sinus separate, the developing bladder remains connected to the allantois through a connection called the urachus.
- Persistence of this communication leads to urachal remnants.
- The urachal remnant anomalies include:
  - Patent urachus
  - Urachal sinus
  - Urachal cyst
  - Urachal diverticulum
- Subsequently, the yolk and body stalks fuse to become the umbilical cord.
- Development of the abdominal wall narrows the umbilical ring, which should close before birth.
- Persistence of the umbilical ring results in an umbilical hernia.

16.3 Classification

- There are four types of congenital urachal remnant anomalies.
- They are:
  - Patent urachuss(50 %)
  - Urachal cyst (30 %)
  - Urachal-umbilical sinus (15 %)
  - Vesicourachal diverticulum (5 %)
- Urachal cyst:
  - A urachal cyst is a cyst which occurs in a persistent portion of the urachus between the umbilicus and the urinary bladder.
  - It presents as an extraperitoneal mass in the umbilical region.
  - Urachal cysts are usually silent clinically until infection, calculi or adenocarcinoma develop
  - It is characterized by:
    - Abdominal pain, and fever if infected
    - It may rupture, leading to peritonitis
    - It may drain through the umbilicus.

- Patent urachus:
  - This is the commonest congenital malformation of the urachus.
  - In patent urachus, the whole urachus fails to obliterate and there is a patent communication between the urinary bladder and the umbilicus.
- Umbilical sinus:
  - In umbilical sinus, the distal part of the urachus remains open to the umbilicus.
  - The usual presentation is persistent umbilical discharge.
- Vesico-urachal diverticulum:
  - In this, there is a wide patent urachal opening to the urinary bladder
- Inflammation and malignancy are the commonest complications of urachal remnants.
- Inflammation occurs more frequently in children and young adults.
  - Inflammation may be complicated by the development of an abscess which can remain clinically unrecognized or it can present as acute surgical abdomen.
  - This must be kept in mind as the diagnosis often is confused with other diseases such as Meckel's diverticulum, acute appendicitis, recurrent urinary infections, or abdominal colicky pain of unknown origin.
    - The most common infecting pathogens are *E. coli* and *Proteus*, but a variety of other pathogens can also be found, including *Staphylococcus aureus*, *Bacteroides*, *Fusobacterium*, and *Streptococcus iridans*.
    - Rarely it is secondary to *Actinomycosis*, *Aspergillus* or *Tinea corporis*.
    - Occasionally, a chronic inflammatory process can result in the unusual form of a xanthogranulomatous urachitis
  - Patients may also complain of urinary symptoms such as suprapubic pain, dysuria, and/or intermittent episodes of urinary retention.
  - Infection of a urachal sinus and the cord stump must be taken seriously because of its potential sequelae such as cellulitis, necrotizing fasciitis, peritonitis, multiple hepatic abscess, septicaemia, and possible retroperitoneal abscess.

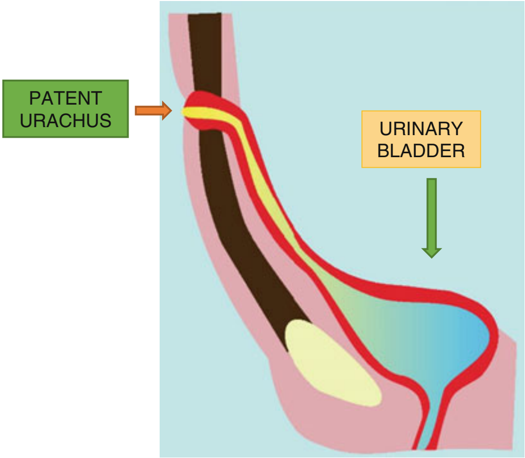
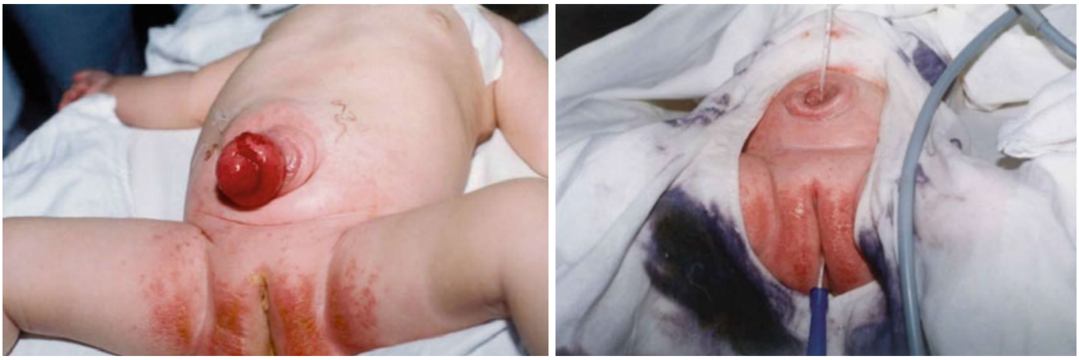


Fig. 16.4 Diagrammatic representation of a patent urachus

- Malignant degeneration of urachal remnants occurs more frequently in middle-aged and older people.

16.4 Clinical Features

- Congenital urachal anomalies are rare and occur more common in males than females (M:F is 2:1).
- The majority of patients with urachal abnormalities (except those with a patent urachus) are asymptomatic.
- However, they may become symptomatic if these abnormalities are infected.
- Patent urachus (Figs. 16.4, 16.5, and 16.6):
  - If a persistent communication remains between the bladder lumen and the umbilicus, urine leakage is usually noted during the neonatal period.
  - In about one-third of cases, this condition is associated with posterior urethral valves or urethral atresia.
  - Some patients with patent urachus are asymptomatic, and sometimes an acquired obstructive lesion of the lower urinary tract may result in umbilical-urinary fistulas.
  - A definitive diagnosis can be made with sinography or cystography.
  - Patent urachus can also be demonstrated at longitudinal US and occasionally at CT performed in infants during the bladder-filling stage.



Figs. 16.5 and 16.6 Clinical photographs showing patent urachus. Note the catheter inserted through the urethra and coming out through the patent urachus. Not also the prolapsing urachus in the first photograph

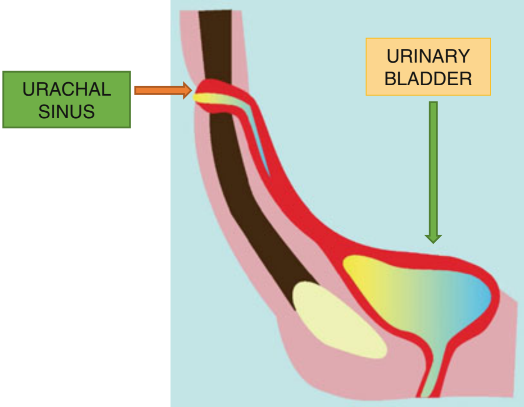


Fig. 16.7 Diagrammatic representation of a urachal sinus

- Umbilical-urachal sinus (Figs. 16.7):
  - – Umbilical-urachal sinus consists of blind dilatation of the urachus at the umbilical end.
  - – A small opening into the umbilicus is generally present.
  - – This may result in periodic umbilical discharge.
- Vesicourachal diverticulum may Vesicourachal diverticulum (Fig. 16.8):
  - – In vesicourachal diverticulum, the urachus communicates only with the bladder dome.
  - – This condition results when the vesical end of the urachus fails to close.
  - – Vesicourachal diverticulum is asymptomatic in most cases.
  - – It tends to be found in patients with chronic bladder outlet obstruction.
  - – be complicated by:
    - Urinary tract infection

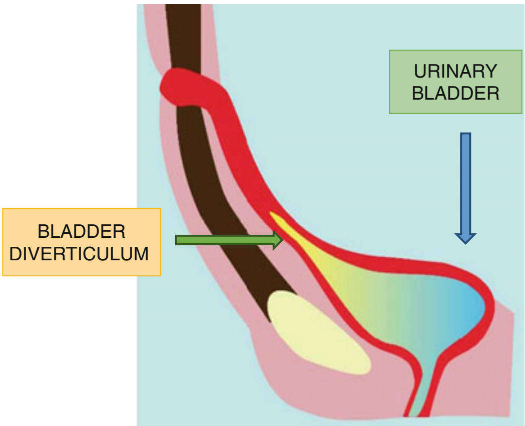


Fig. 16.8 Diagrammatic representation of a vesicourachal diverticulum

    - Intraurachal stone formation
    - Increased prevalence of carcinoma after puberty
  - – It is usually discovered incidentally at axial CT performed for unrelated reasons. It appears as a midline cystic lesion just above the anterosuperior aspect of the bladder.
  - – On US, it appears as an extraluminally protruding, fluid-filled sac that does not communicate with the umbilicus.
  - – In infants, vesicourachal diverticulum is commonly accompanied by prune-belly syndrome.
- Urachal cyst (Figs. 16.9, 16.10, 16.11, 16.12, and 16.13):
- – An urachal cyst develops if the urachus closes at both the umbilicus and the bladder but remains patent between these two endpoints.

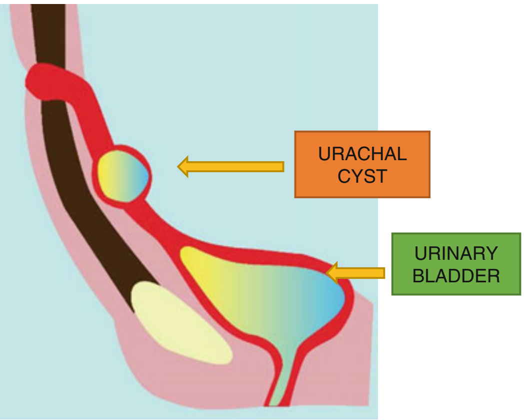


Fig. 16.9 Diagrammatic representation of a urachal cyst

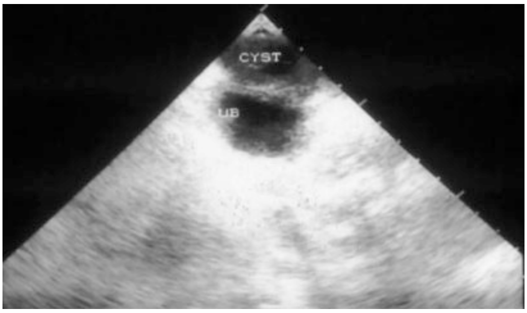
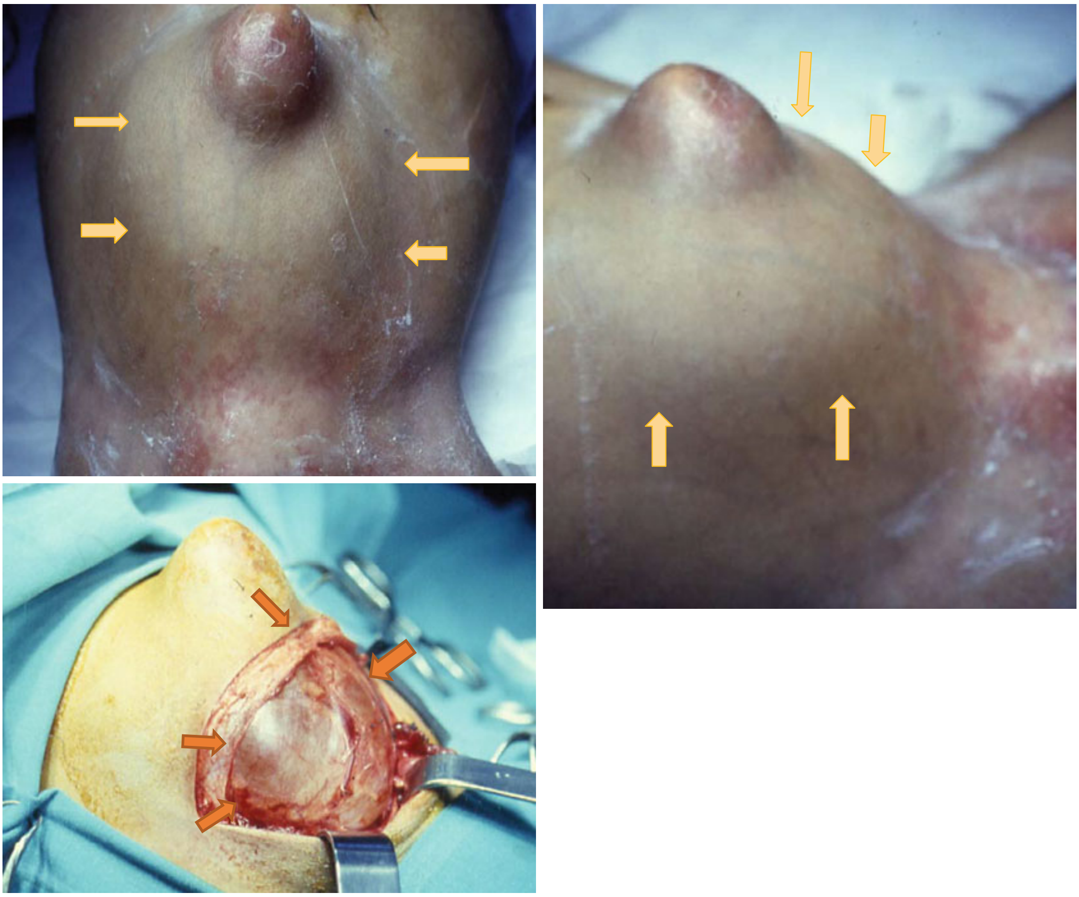


Fig. 16.10 Abdominal ultrasound showing a urachal cyst

- It occurs primarily in the lower one-third of the urachus and less frequently in the upper one-third.
- Urachal cysts are usually small but vary considerably in size.
- They become symptomatic when they enlarge.
- Sometimes, they are found as incidental masses during routine examination.
- As with other urachal anomalies, infection is the most common complication of urachal cyst, and the majority of cysts are infected at the time of diagnosis.
- Rarely, spontaneous rupture of an infected cyst into the abdominal cavity leads to localized or generalized peritonitis.
- Percutaneous needle biopsy or fluid aspiration is mandatory for diagnosis and treatment.
- Total exciton of the cyst is essential because there is a 30 % reinfection rate and carcinoma may develop in an unresected or incompletely resected urachal. cyst.
- CT or US are helpful for the diagnosis and shows a fluid-filled cavity in the midline lower abdominal wall.
- Eggshell calcification of the cyst wall is rarely seen.
- Infected urachal cyst manifests as wall thickening and demonstrates an attenuation higher than that of water at CT and soft-tissue components and mixed echogenicity at US.

16.5 Tumors and Urachal Remnants

- Urachal tumors are extremely rare and can be benign or malignant.
- Benign urachal tumors include:
  - Adenomas
  - Fibromas
  - Fibroadenomas
  - Fibromyomas
  - Hamartomas
- Malignant urachal neoplasms represent less than 0.5 % of all urinary bladder cancers.
- The normal urachus is commonly lined by transitional epithelium, but it was found that urachal carcinoma predominantly are adenocarcinoma (90 % of cases) and 75 % of these cases are mucin producing.
- This is probably due to the metaplasia of the urachal mucosa into columnar epithelium followed by malignant transformation.
- The remaining urachal carcinomas are transitional, squamous, or anaplastic carcinomas.
- 34 % of bladder adenocarcinomas are of urachal origin.
- These tumors are most commonly seen in patients 40–70 years of age, two-thirds of whom are men.
- Urachal carcinomas may be solid, cystic, or a combination of the two.
- Urachal tumors are typically silent because of their extraperitoneal location.
- The majority of patients exhibit local invasion or metastatic disease at presentation.
- Ninety percent of urachal carcinomas arise in the juxta vesical portion of the urachus and



Figs. 16.11, 16.12, and 16.13 Clinical photograph showing a patient with urachal cyst being excised. Note the location of the cyst above the urinary bladder and beneath the anterior abdominal wall

extend superiorly toward the umbilicus and inferiorly through the bladder wall.

- A minority of urachal carcinomas are located in the middle of the urachus (6 % of cases) or near the umbilical end (4 %).
- 50–70 % of urachal carcinomas produce psammomatous calcifications that may be punctate, stippled, or curvilinear and peripheral.
- The prognosis is generally poor because these tumors are usually clinically silent and discovered late after it has reached a large size and extended locally or metastasized. Metastases occur initially in the pelvic lymph nodes, followed by systemic metastases to the lung, brain, liver, and bone.
- It was shown that many of the features of urachal remnants, including congenital lesions with or without superimposed infection and tumors, can be easily demonstrated by abdominal ultrasound.
- CT is more helpful in confirming the diagnosis and determining the extent of the disease.

16.6 Management

- Asymptomatic remnants are managed conservatively.
- Surgical excision should be avoided for patients younger than 1 year because the remnant might spontaneously disappear.
- Infective complications of urachal remnants are treated with antibiotic therapy for the acute infection followed by surgical excision

- The presence of an abscess requires drainage preferably percutaneous drainage under ultrasound guidance and once the infection subsides, the remnant should be excised.
- It was reported that up to 30 % of infected urachal cysts recurred when not excised.
- It is generally recommended that all urachal remnants should be excised to avoid recurrent infection and because of possible malignant transformation later in life.
- Surgical excision is usually done through a transverse or midline infra-umbilical incision.
- Recently and as a result of advances in minimal invasive surgery, laparoscopic excision of urachal remnants was shown to be feasible and safe. The advantages of laparoscopic excision of urachal remnants include:
  - It minimizes the morbidity associated with open surgery
  - A shorter hospital stay
  - Faster recovery
  - Better cosmetic result

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17 Inguinal Hernias and Hydroceles

17.1 Introduction

- Hippocrates used the Greek *hernios* for bud or bulge to describe abdominal hernias.
- Abdominal wall hernias are protrusions of abdominal contents through a defect or weakness in the abdominal wall.
- Abdominal wall hernias are among the most common of all surgical problems in infants and children.
- There are several different types of abdominal wall hernias in infants and children including:
  - Inguinal hernia
  - Umbilical hernia
  - Paraumbilical hernia
  - Epigastric hernia
  - Femoral hernia
  - Spigelian hernia
  - Lumbar hernia
  - Incisional hernia
  - Other rare hernias
- The management of abdominal wall hernias are different and depend on the type of hernia, age of the patient and mode of presentation.
- All pediatric inguinal hernias require operative treatment to prevent the development of complications, such as inguinal hernia incarceration or strangulation.

17.2 Inguinal Hernia

17.2.1 Incidence

- The exact incidence of indirect inguinal hernia in infants and children is unknown.
- The incidence of hernias is about 10–20 per 1,000 live births and is much more common in prematures.
- Indirect inguinal hernias are more common on the right side and about 60 % of hernias occur on the right side (Figs. 17.1 and 17.2).
- Premature infants are at increased risk for inguinal hernia, with incidence rates of 2 % in females and 7–30 % in males.
- Approximately 5 % of all males develop a hernia during their lifetime.
- Inguinal hernias are much more common in males than in females.
- The male-to-female ratio is estimated to be 4–8:1.
- Moreover, the risk of incarceration of inguinal hernia is more than 60 % in prematures.
- Inguinal hernias:
  - 60 % are on the right side.
  - 30 % are on the left side.
  - 10 % are bilateral (Figs. 17.3 and 17.4)
  - Anatomically speaking, indirect and direct inguinal hernias differ in that the direct

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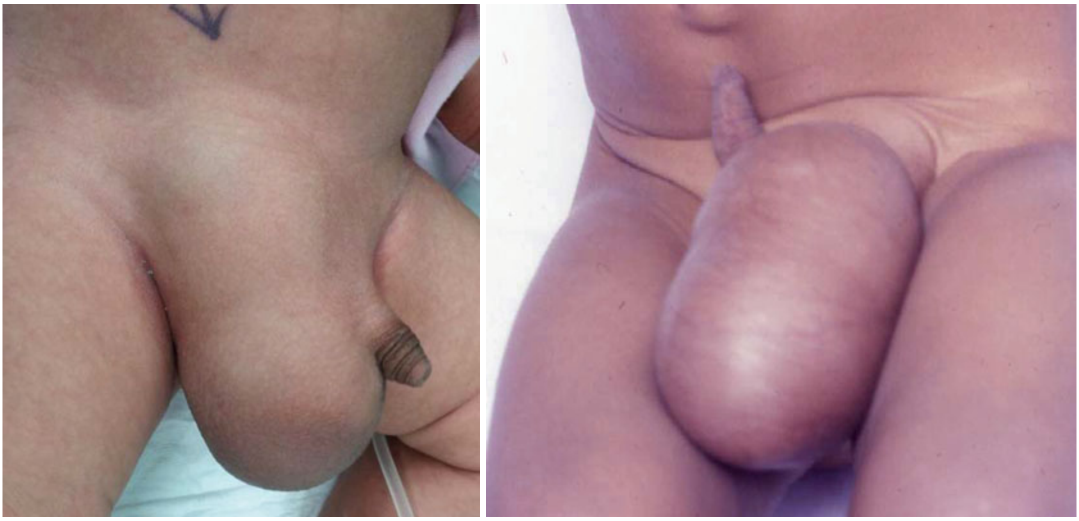
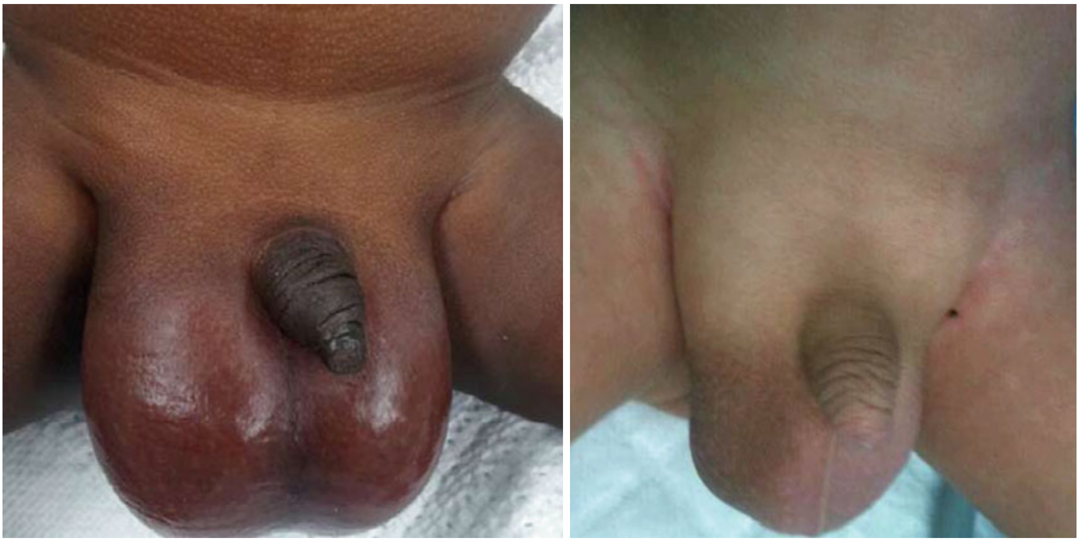


Figs. 17.1 and 17.2 Clinical photographs showing a large right and left inguinal hernia



Figs. 17.3 and 17.4 A clinical photograph showing bilateral inguinal hernias

hernia bulges through the inguinal floor medial to the inferior epigastric vessels and the indirect hernia arises lateral to the inferior epigastric vessels.

– Inguinal hernia can be complete where the whole sac descends into the scrotum and surrounds the tesis (Scrotal hernia) or incomplete where the hernial sac ends up in the inguinal canal above the testis (Inguinal hernia) (Fig. 17.5).

17.2.2 Etiology

- Inguinal hernias are congenital.
- Embryologically, the processus vaginalis is an outpouching of peritoneum attached to the testicle that trails behind as it descends retroperitoneally into the scrotum.
- Normally, the processus vaginalis obliterates.
- When obliteration of the processus vaginalis fails to occur, inguinal hernia results.

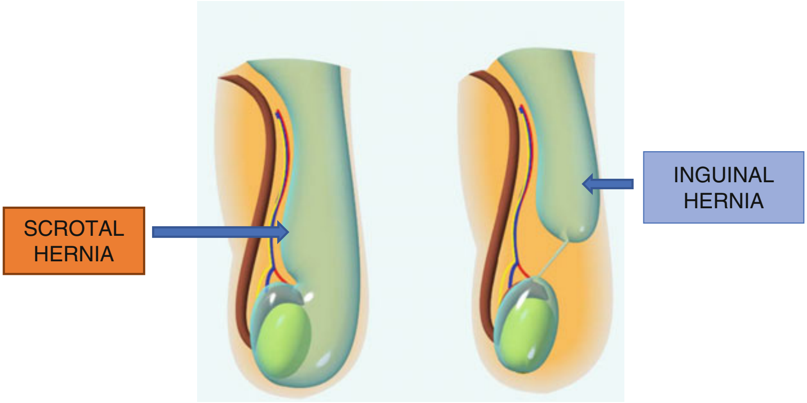


Fig. 17.5 Diagrammatic representation of the classic inguinal hernia and inguinal hernia extending into the scrotum (scrotal hernia)

- Increased intra-abdominal pressure is seen in a variety of conditions and also contribute to the appearance of inguinal hernia.
- Elevated intra-abdominal pressure is associated with chronic cough, ascites, increased peritoneal fluid from biliary atresia, peritoneal dialysis or ventriculoperitoneal shunts, intraperitoneal masses or organomegaly, and constipation.
- Other conditions with increased incidence of inguinal hernias are:
  – Exstrophy of bladder.
  – Neonatal intraventricular hemorrhage.
  – Myelomeningocele.
  – Undescended testes.
- The following conditions are associated with an increased risk of inguinal hernia:
  – Prematurity and low birth weight.
  – Urologic conditions:
    - Cryptorchidism
    - Hypospadias
    - Epispadias
    - Exstrophy of the bladder
    - Ambiguous genitalia
    - Cloacal exstrophy
  – Patent processus vaginalis, which may be present because of increased intraabdominal pressure due to ventriculoperitoneal shunts, peritoneal dialysis, or ascites
  – Abdominal wall defects
    - Gastroschisis
    - Omphalocele
  – Family history
  – Meconium peritonitis
  – Cystic fibrosis
  – Connective tissue disease
  – Mucopolysaccharidosis
  – Congenital dislocation of the hip
  – Ehlers-Danlos syndrome
  – Marfan syndrome
  – Fetal hydrops
  – Liver disease with ascites
  – Ventriculoperitoneal shunting for hydrocephalus

17.2.3 Clinical Features

- The parents of infants and children with an inguinal hernia present with the history of a swelling that is commonly intermittent, in the inguino-scrotal region in boys and inguino-labial region in girls.
- The swelling commonly occurs after crying or straining.
- Sometimes, they present with an obvious swelling at the inguinal region or sometimes within the scrotum in boys (Fig. 17.6).
- The hernia may be bilateral (Figs. 17.7 and 17.8)
- The swelling is painless and reducible in a simple inguinal hernia.
- The presence of a painful swelling suggests an incarcerated inguinal hernia.
- Patients with an incarcerated hernia generally present with a tender firm mass in the inguinal canal or scrotum that is irreducible.

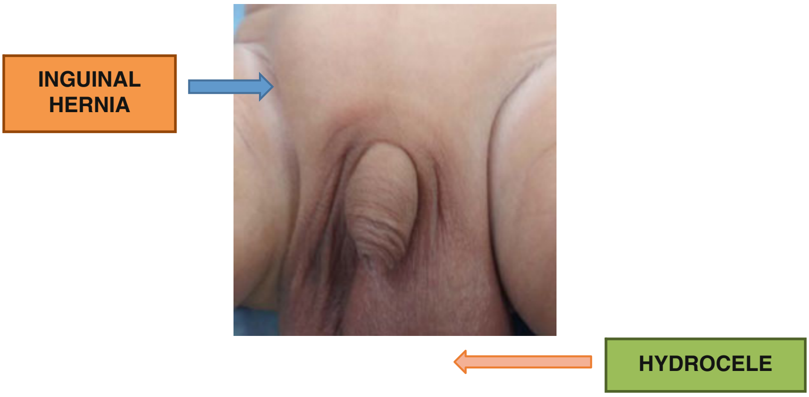
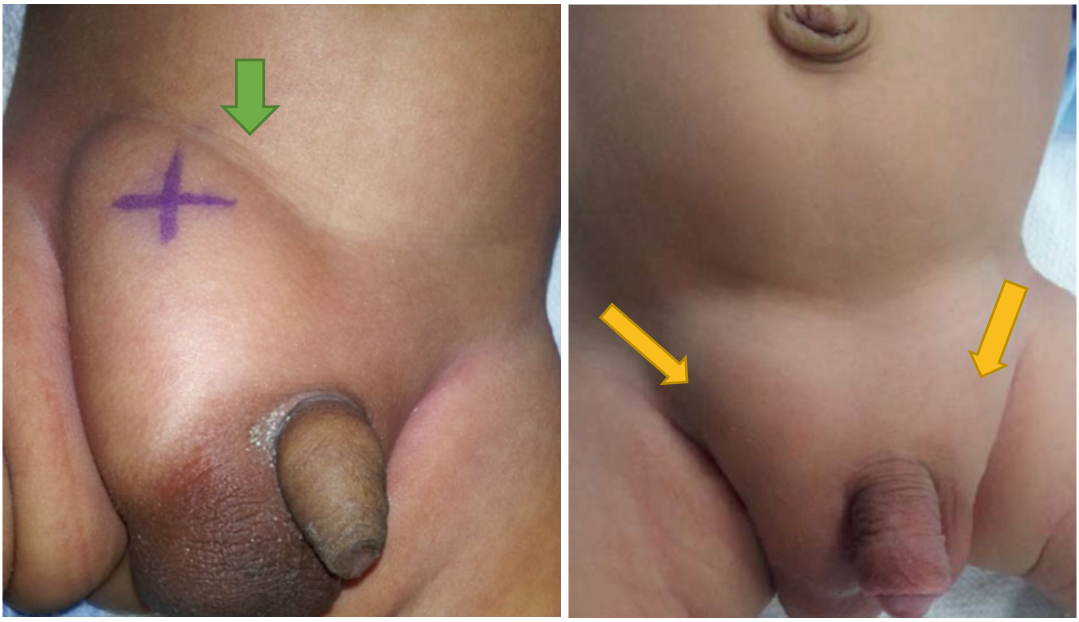


Fig. 17.6 A clinical photograph showing an incarcerated right inguinal hernia. Note also the left hydrocele



Figs. 17.7 and 17.8 Clinical photographs showing bilateral incarcerated inguinal hernia

- Silk sign: When the hernia sac is palpated over the cord structures, the sensation may be similar to that of rubbing two layers of silk together.
- This finding is known as the silk sign and is highly suggestive of an inguinal hernia.

17.2.4 Variants of Hernia

1. Indirect inguinal hernia:
    - Indirect inguinal hernias occur when the abdominal contents protrude through the deep inguinal ring, lateral to the inferior epigastric vessels.

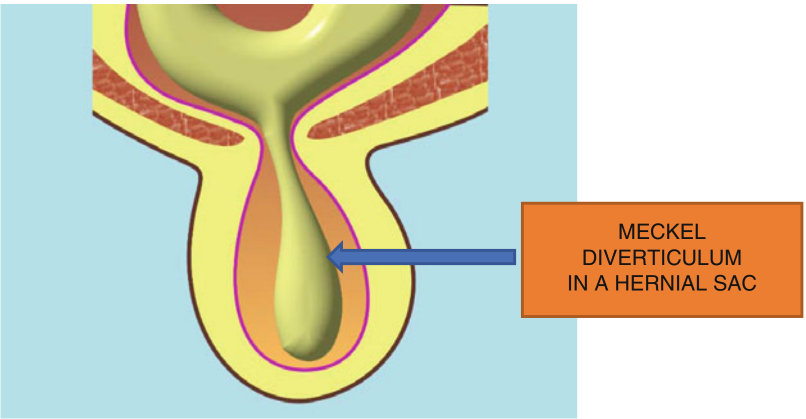


Fig. 17.9 Diagrammatic representation of a Littre' hernia

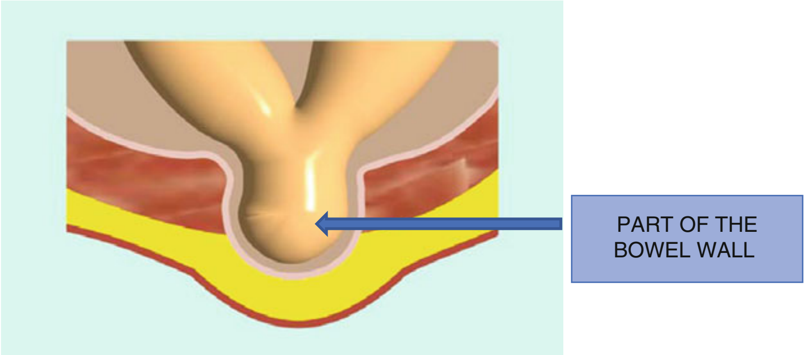


Fig. 17.10 Diagrammatic representation of a Richter's hernia

- It is caused by failure of embryonic closure of the processus vaginalis.

2. Direct inguinal hernia:
   - This type of inguinal hernia, enters through a weak point in the transversalis fascia of the abdominal wall, and its sac is noted to be medial to the inferior epigastric vessels.
   - Direct inguinal hernias may occur in males or females, but males are ten times more likely to get a direct inguinal hernia.
   - These hernias are capable of exiting via the superficial inguinal ring but, unlike indirect inguinal hernias, they cannot descend into the scrotum.
3. Littre's hernia (Fig. 17.9):
   - A Littre's hernia is a hernia containing a Meckel's diverticulum.
   - Littre's hernia was first described by the French surgeon Alexis Littré in 1700.
   - He described three cases from cadaverous studies of incarcerated femoral hernias containing a diverticulum of the small bowel.
4. Sliding inguinal hernia:
   - A sliding inguinal hernia occurs when the wall of the hernia sac is made up of an organ like the urinary bladder or colon.
   - It is a variant that is seen in 3 % of hernia cases.
5. Richter's hernia (Fig. 17.10):
   - A Richter's hernia occurs when the antimesenteric wall of the intestine protrudes through a hernial defect.
   - The first scientific description of this hernia was by August Gottlob Richter in 1778.
   - A Richter's hernia can result in strangulation and necrosis in the absence of intestinal obstruction.
   - It is a relatively rare but dangerous type of hernia.
6. Busse's hernia (Fig. 17.11):
   - An inguinal hernia in which the testicle is within the hernia sac.

7. Maydl's hernia (Fig. 17.12):
   - This is seen when two adjacent loops of small intestines are within a hernial sac with a tight neck.
   - The intervening portion of bowel lies within the abdomen

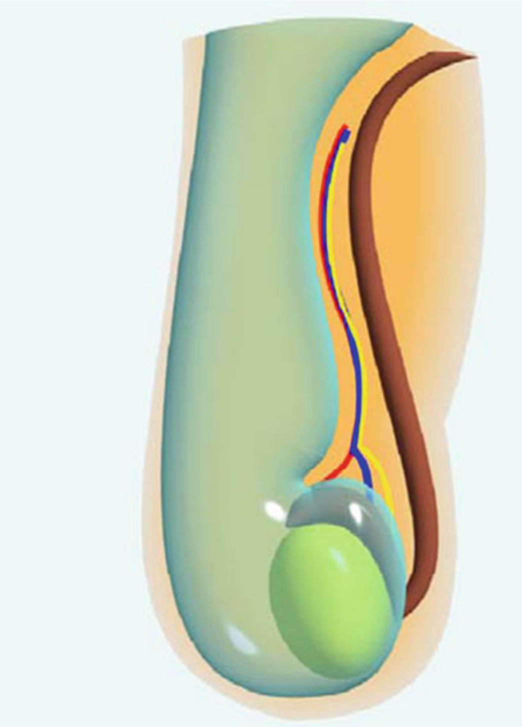


Fig. 17.11 Diagrammatic representation of Busse's hernia

   - This intervening portion of bowel becomes deprived of its blood supply and eventually becomes ischemic and necrotic.
   - Perforation of this part of intestine will lead to peritonitis and the patient present with an acute abdomen.
8. Amyand's hernia (Fig. 17.13):
   - The content of the hernial sac is the vermiform appendix.

17.2.5 Complications of Inguinal Hernias

1. Incarceration:
   - The herniated bowel in inguinal hernia can become swollen, edematous and engorged within the hernial sac.
   - The hernia becomes irreducible and causes intestinal obstruction in infants and children (Figs. 17.14, 17.15, 17.16, and 17.17).
   - Every attempt should be made to reduce it manually.
   - Incarceration occurs in 17 % of right-sided hernias and 7 % of left-sided hernias.
   - More than 50 % of cases of incarceration occur within the first 6 months of life; the risk gradually decreases after age 1 year.
   - Premature infants have twice the risk of incarceration than the general pediatric population.

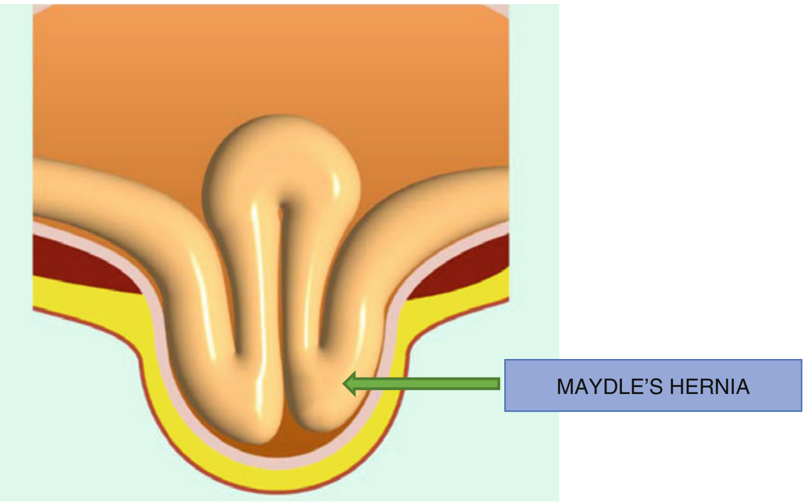
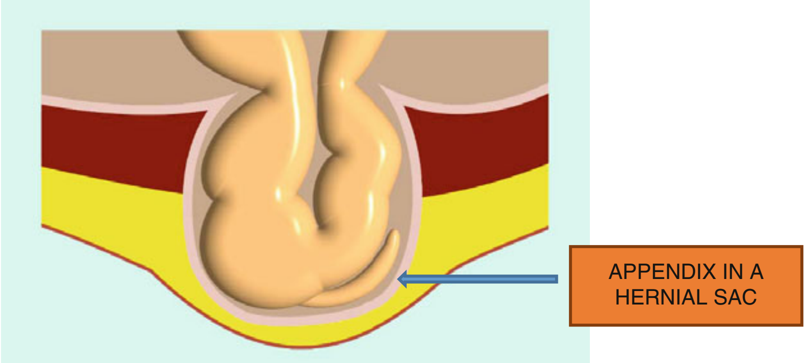
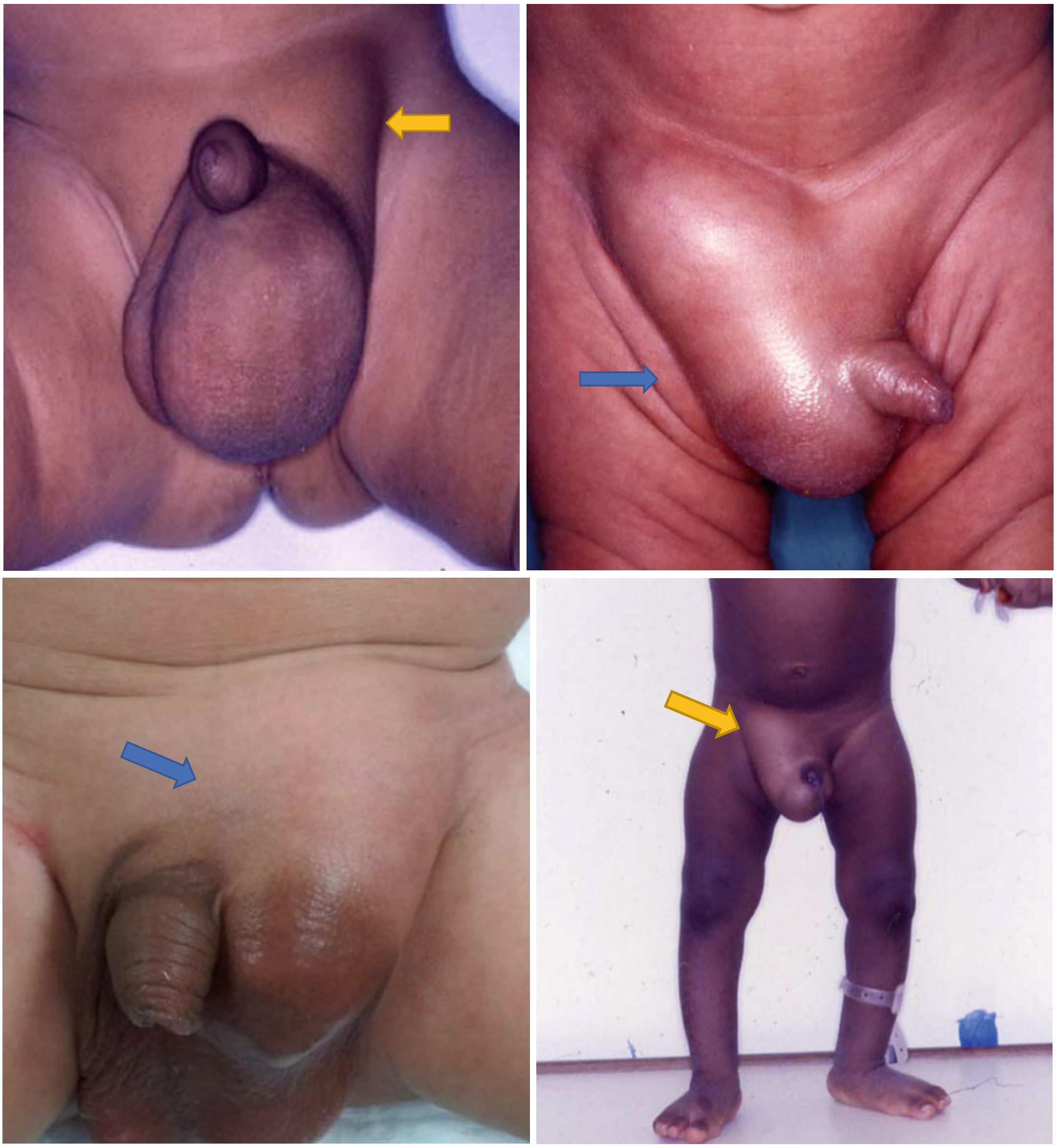


Fig. 17.12 A diagrammatic representation of Maydle's hernia

Fig. 17.13 A diagrammatic representation of Amyand's hernia


APPENDIX IN A HERNIAL SAC



Figs. 17.14, 17.15, 17.16, and 17.17 Clinical photographs showing irreducible inguinal hernias

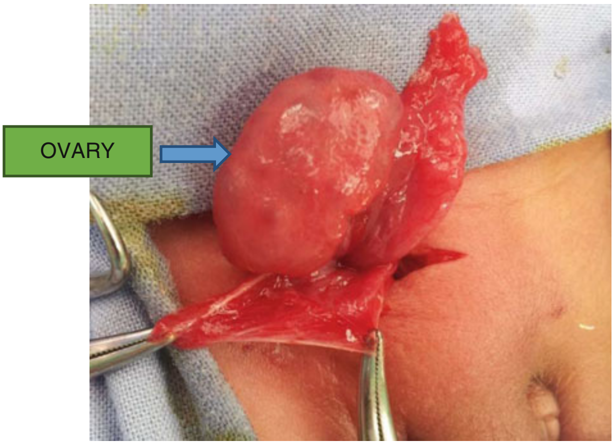


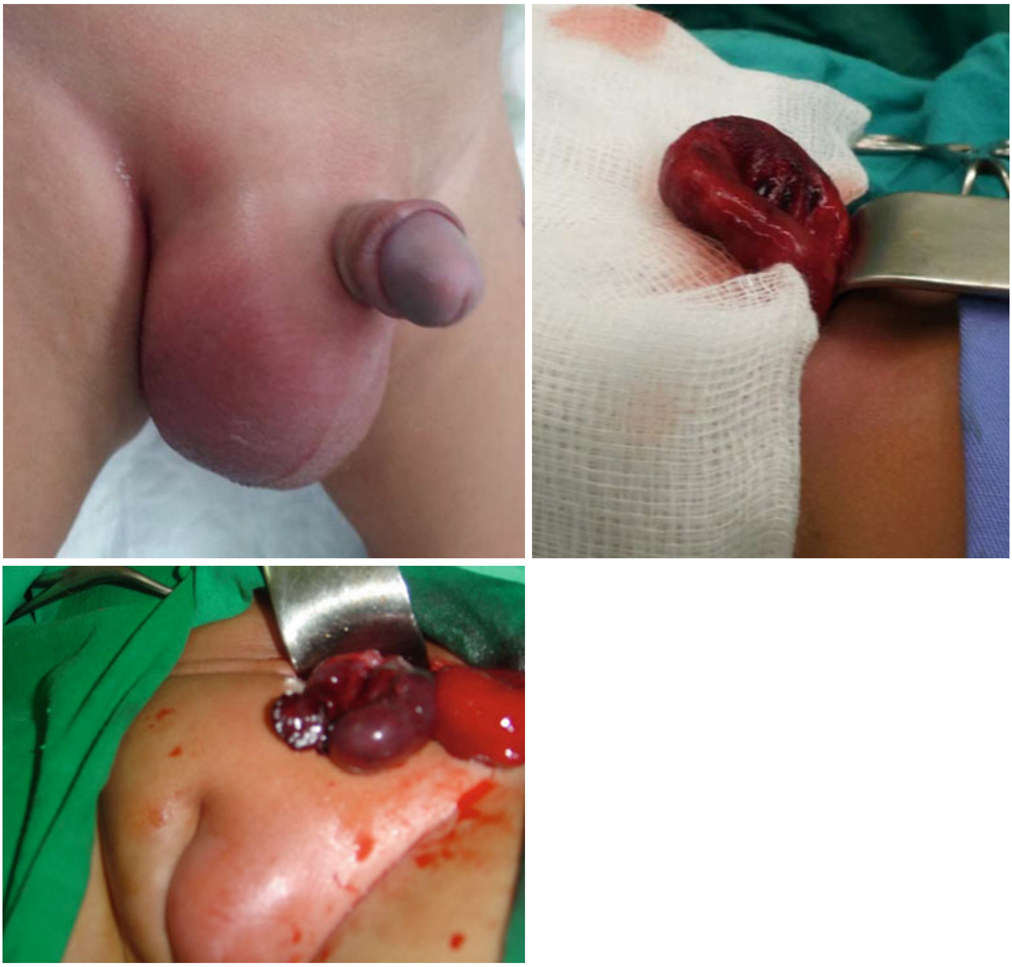
Fig. 17.18 An intraoperative photograph showing irreducible hernia containing the ovary which was swollen

- More than two thirds of all incarcerations occur in children younger than 1 year.
- Girls are more likely to develop incarceration of an inguinal hernia; the incidence in girls is 17.2 %, whereas the incidence in boys is 12 % (Fig. 17.18).

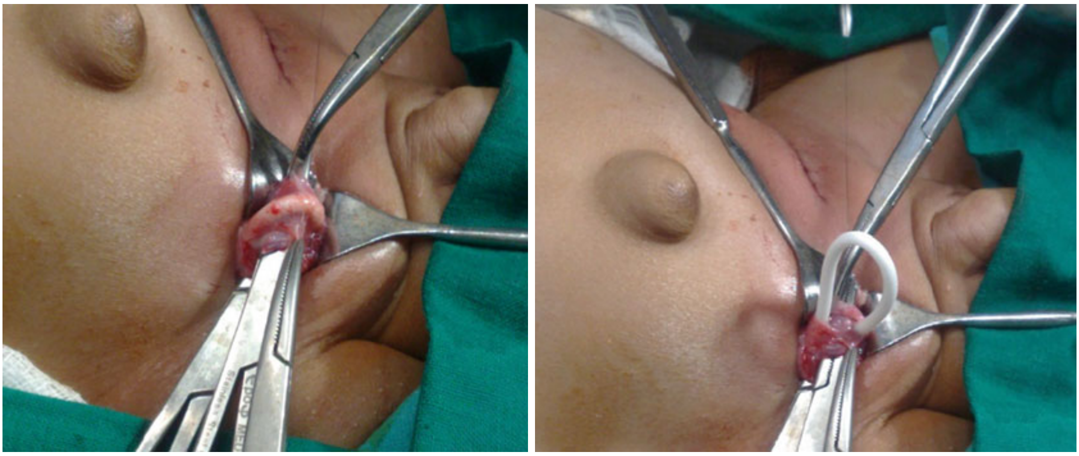
2. Strangulation (Figs. 17.19, 17.20, and 17.21):
   - Once the vascular supply of the herniated contents becomes compromised, the hernia becomes strangulated.
   - This may lead to ischemic necrosis and intestinal perforation.
   - This is an indication for emergency surgical exploration.
   - A rare complication of inguinal hernia is migration of ventriculoperitoneal shunt into the hernial sac (Figs. 17.22 and 17.23).

17.2.6 Treatment

- All pediatric inguinal hernias require operative treatment to prevent the development of complications, such as incarceration or strangulation.
- Most inguinal herniatomies are performed on an outpatient basis.
- Laparoscopic hernia repair in children is not performed as commonly as in adults.
- Contralateral inguinal hernia exploration:
  - There is controversy about whether the contralateral groin should be explored.
  - Today, most surgeons do not routinely perform a contralateral exploration unless a contralateral inguinal hernia or patent processus vaginalis can be demonstrated either by preoperative ultrasonography or intraoperative laparoscopy.
  - A hernia develops in the other side of the groin in up to 30 % of children who have had hernia surgery. This is more so if the initial hernia was on the left side.
  - When an inguinal hernia is present, some pediatric surgeons perform a contralateral groin exploration.
  - This is to detect an occult patent processus vaginalis that may lead to a hernia on the opposite side (metachronous contralateral hernia). This is present in less than 5 % of cases.
  - The Goldstein test can be used to determine when to perform a contralateral exploration. In this test, the abdomen is insufflated with gas through the already open hernia sac. Crepitus in the opposite groin is a positive test result, suggesting a contralateral patent processus vaginalis and warranting a contralateral exploration. This test may not be conclusive.
  - An alternative approach is laparoscopy which can be used to detect an occult contralateral patent processus vaginalis.
  - This can be done through a separate incision at the umbilicus or through the already opened hernia sac. This allows inspection of the contralateral inguinal ring and assessment of its patency.



Figs. 17.19, 17.20, and 17.21 Clinical photographs showing a strangulated inguinal hernia. Note the colour of the intestine as a result of strangulation and the strangulated gangrenous ovary



Figs. 17.22 and 17.23 Clinical intraoperative photographs showing a ventriculoperitoneal shunt in the inguinal hernial sac

17.2.7 Complications of Inguinal Herniotomy

- The overall operative complication rate associated with hernias is 1.7–8 %.
- Infertility:
  - Infertility may result from bilateral injury to the vas deferens or injury to the vas of a solitary testis.
  - The presence of a vas-like structure in the pathology specimen does not necessarily indicate injury to the vas, as up to 6 % of specimens contain müllerian ductal remnants with a histologic appearance very similar to the vas.
- Testicular atrophy:
  - An incarcerated hernia may compromise blood flow to the testicle prior to surgery.
  - The rate of testicular atrophy after repair of an incarcerated hernia can be as high as 19 %.
  - Testicular atrophy may also result from intraoperative injury to the testicular blood supply.
- Scrotal hematoma:
  - As with any surgery, scrotal hematomas may occur.
  - A hematoma usually does not need to be explored unless the hematoma continues to enlarge or becomes infected.
  - Treatment is with scrotal elevation and analgesics.
- Wound infection.
- Hypesthesia and neuropathic pain can result from nerve entrapment or injury.
- Iatrogenic cryptorchidism:
  - This may result from excessive scar formation and ascent of the testicle.
  - Or improper replacement of the testicle into the scrotum after herniotomy.
- Recurrence and hydrocele formation:
  - This may be seen in less than 5 % of cases.
  - If the hydrocele does not disappear spontaneously after 1 year, reoperation is indicated.
  - With open surgery, ipsilateral recurrence rates are less than 1 %.
  - The ipsilateral recurrence rate following laparoscopic inguinal hernia repair is 3.4 %.
- The occurrence of a metachronous contralateral hernia is inversely related to age and can be as high as 12 %. This is more so if the initial hernia was on the left side.

17.3 Hydrocele

17.3.1 Embryology

- During fetal development, the testicle develops below the kidney, within the peritoneal cavity.
- Subsequently, the testicle descends down and through the inguinal canal and finally into the scrotum.
- During its descent, it is accompanied by an extension of peritoneum (the processus vaginalis).
- Normally, the processus vaginalis obliterates and becomes a fibrous cord.
- The distal part of the processus vaginalis forms the tunica vaginalis. In postnatal life, this is a potential space that should not communicate with the peritoneal cavity of the abdomen.
- If the processus vaginalis does not close, it is referred to as a patent processus vaginalis.
- If the patent processus vaginalis is small in caliber and allow fluid to pass from the abdomen, the condition is referred to as a communicating hydrocele.
- If the patent processus vaginalis is larger, allowing ovary, intestine, omentum, or other abdominal contents to protrude, the condition is referred to as a hernia.
- A hydrocele usually transilluminates on examination. However, gas-filled intestines also transilluminate. This must be considered during evaluation (Fig. 17.24).
- Hydroceles can be unilateral or bilateral (Figs. 17.25, 17.26, and 17.27)
- An important point differentiating a hydrocele from an inguinal hernia is that you can get above a hydrocele but you cannot get above an inguinal hernia. The only exception to this is an abdomino-scrotal hydrocele.

17.3.2 Classification of Hydroceles (Fig. 17.28)

- Communicating hydroceles:
  - The patent processus vaginalis is continuous with the tunica vaginalis, which surrounds the testicle.
  - The communication is small, so only fluid can pass into the patent processus vaginalis.
  - A characteristic feature of communicating hydroceles is their tendency to be relatively small in the morning and increase in size during the day.
  - Actions which increase intra-abdominal pressure (crying, coughing, etc.) will also lead to increase in the size of the hydrocele.
- Noncommunicating hydroceles:
  - In this, the fluid is confined to the scrotum within the tunica vaginalis.
  - The processus vaginalis is obliterated so the fluid does not communicate with the abdominal cavity.
  - Such hydroceles are common in infants, and the hydrocele disappears before the infant is 1 year old.

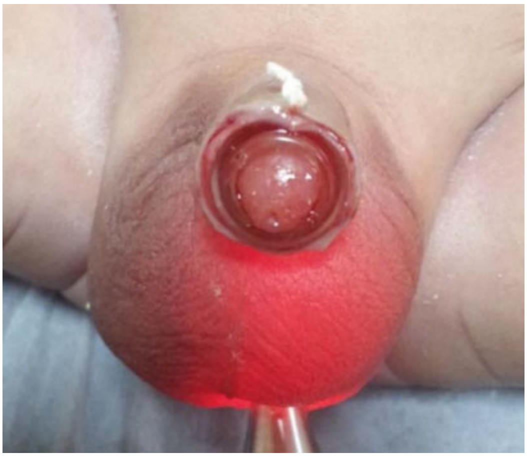


Fig. 17.24 A clinical photograph showing tansillumination of a hydrocele

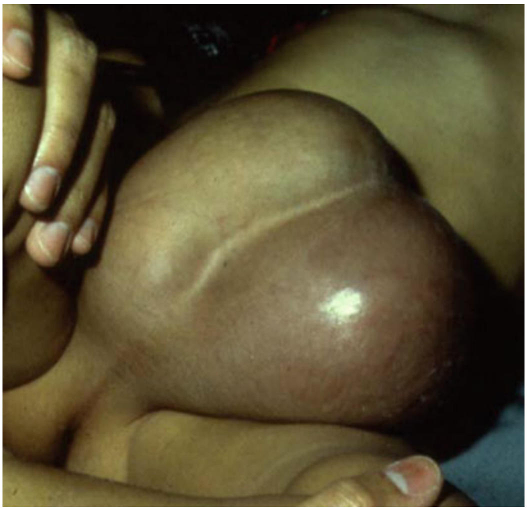
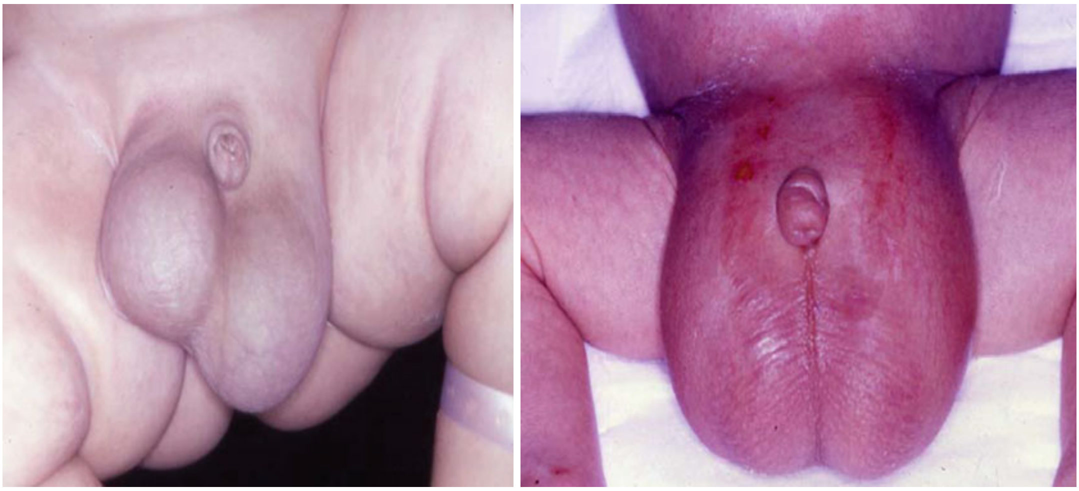


Fig. 17.27 A clinical photograph showing giant bilateral hydroceles



Figs. 17.25 and 17.26 Clinical photographs showing small and large bilateral hydroceles

  - They may be present at birth or develop in older children.
  - The fluid in noncommunicating hydroceles is walled off, the size of the hydrocele is generally stable and does not change with change in intra-abdominal pressure.
- Reactive hydroceles:
  - These are noncommunicating hydroceles that develop following trauma or infection.
- Encysted hydrocele of the cord (Figs. 17.29 and 17.30):
  - This is a fluid filled cystic swelling within the inguinal canal.
  - The fluid does not extend into the scrotum.
  - This occurs when the processus vaginalis obliterates above the testicle and a small communication with the peritoneum persists, and the processus vaginalis may be open as far down as the top of the scrotum.
- Hydrocele of the canal of Nuck:
  - This occurs in girls when fluid accumulates within the processus vaginalis in the inguinal canal.

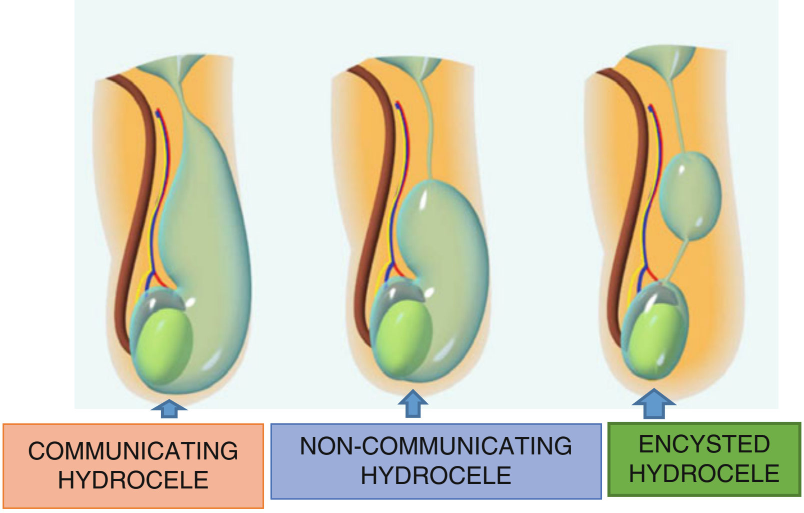
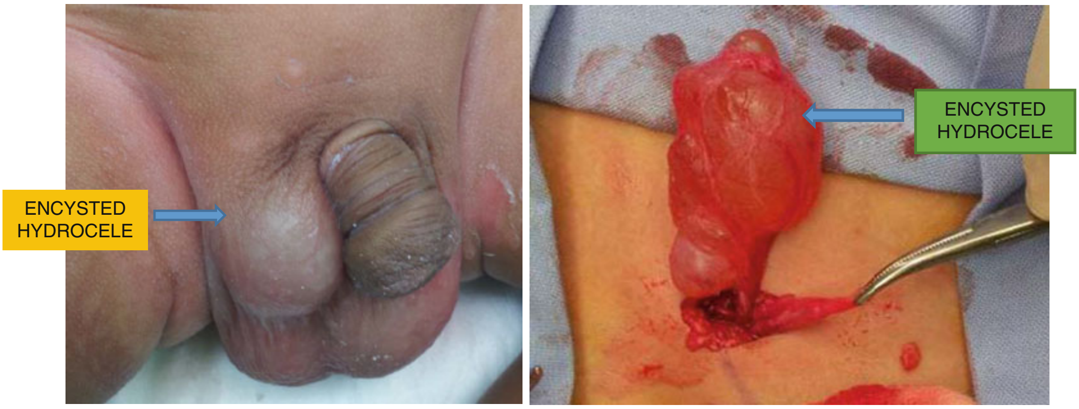

COMMUNICATING HYDROCELE
NON-COMMUNICATING HYDROCELE
ENCYSTED HYDROCELE

Fig. 17.28 A diagrammatic representation of the different types of hydroceles


ENCYSTED HYDROCELE
ENCYSTED HYDROCELE

Figs. 17.29 and 17.30 Clinical and intraoperative photographs showing encysted hydrocele

- Abdomino-scrotal hydrocele:
    - This results from a miniscule opening in the processus vaginalis.
    - The fluid enters the hydrocele and becomes trapped.
    - The hydrocele continues to enlarge and eventually extends upward into the abdomen, causing a fluid-filled mass in the abdomen.

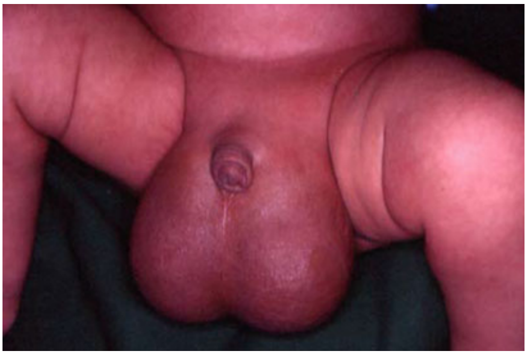
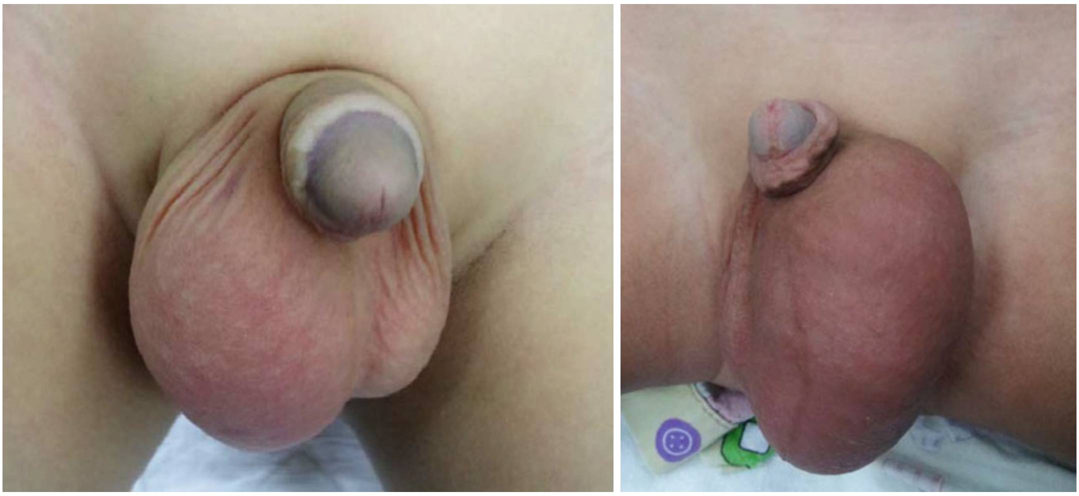


Fig. 17.31 A clinical photograph showing an infant with bilateral hydroceles

17.3.3 Treatment

- Unlike hernias, many newborn hydroceles resolve because of spontaneous closure of the patent processus vaginalis (Figs. 17.31, 17.32, and 17.33).
- The noncommunicating hydrocele:
    - The fluid in the hydrocele is usually reabsorbed before the infant reaches age 1 year.
    - Observation is often appropriate for hydroceles in infants.
- In 95 % of congenital hydroceles, the natural history is one of gradual and complete resolution by 1 year of age.
- For those lasting longer than 1 year or for those non-communicating hydroceles that manifest after the first year, surgical repair is indicated since these rarely resolve spontaneously
- Indications for hydrocele repair:
    - Congenital hydroceles that fails to resolve by age 2 years.
    - Non-communicating hydroceles that manifest after 1 year of age.
    - Continued discomfort and enlargement.
    - Secondary infection (very rare)



Figs. 17.32 and 17.33 Clinical photographs of congenital hydrocele being treated conservatively

Further Reading

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Cloacal Exstrophy

18

18.1 Introduction

- Cloacal exstrophy is an extremely rare and major birth defect representing the severe end of the spectrum of the exstrophy-epispadias complex (Fig. 18.1).
- It is also called vessico-intestinal fissure.
- The exact incidence of cloacal exstrophy is not known but the estimated prevalence ranges from 1 in 50,000 to 250,000 live births.
- It is more common in males than females (a male-female ratio of 2:1).
- Cloacal exstrophy, is also called the OEIS Complex:
  - O: Omphalocele
  - E: Exstrophy of the cloaca
  - I: Imperforate Anus
  - S: Spinal Defects
- Clinically, patients with cloacal exstrophy present at birth and it is characterized by the followings spectrum of anomalies (Figs. 18.2, 18.3, 18.4, 18.5, and 18.6):
  - Two exstrophied hemibladders
  - These are separated by a foreshortened hindgut or cecum
  - The hindgut is often blind-ending resulting in an imperforate anus.
  - This extrophied ileo-cecal region presents between the two hemi bladders (the "elephant trunk" appearance).
  - Omphalocele
  - The associated omphalocele may be major or minor and sometimes no associated omphalocele.
  - Malrotation
  - The symphysis pubis is widely separated
  - The pelvis is often asymmetrically shaped
  - The genitalia (ambiguous genitalia):
    - In males, the penis is divided into two halves usually located separately on either side of the bladder plates with the adjacent scrotal halves.
    - In females, the clitoris is divided into two haves usually located separately on either side of the bladder plates with the adjacent part.
    - Duplication of the vagina and uterus
    - Vaginal agenesis

18.2 Etiology and Pathogenesis

- The exact etiology of cloacal exstrophy is not known.
- Several theories have been proposed to explain the pathogenesis of cloacal exstrophy but none of them can fully explain the spectrum of anomalies seen in cloacal exstrophy.
- The most accepted theory is that cloacal exstrophy results from premature rupture of the cloacal membrane prior to caudal migration of the urorectal septum, and failure of fusion of the genital tubercles.

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A.H. Al-Salem, *An Illustrated Guide to Pediatric Urology*, DOI 10.1007/978-3-319-44182-5_18

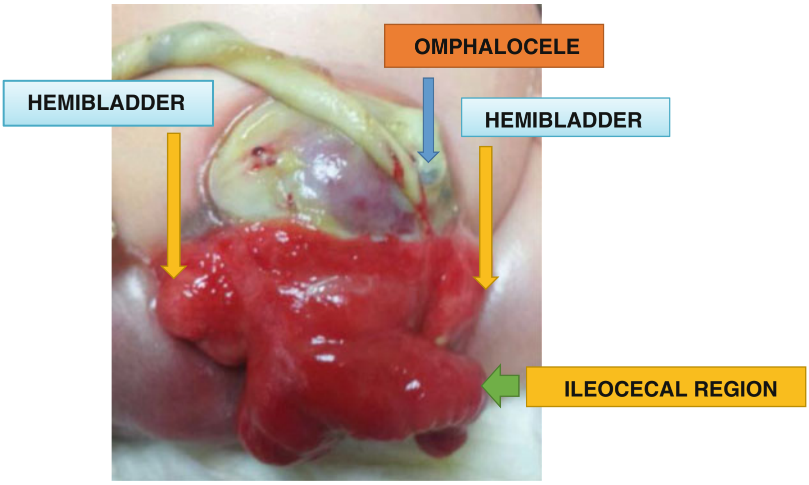
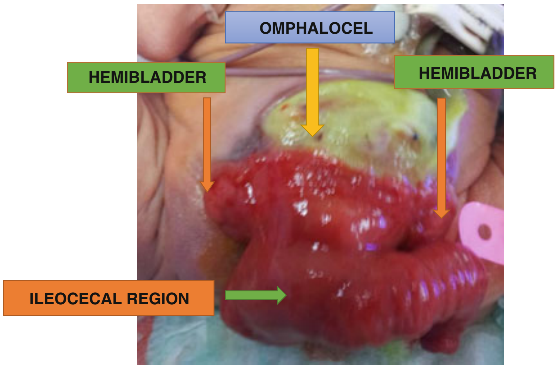
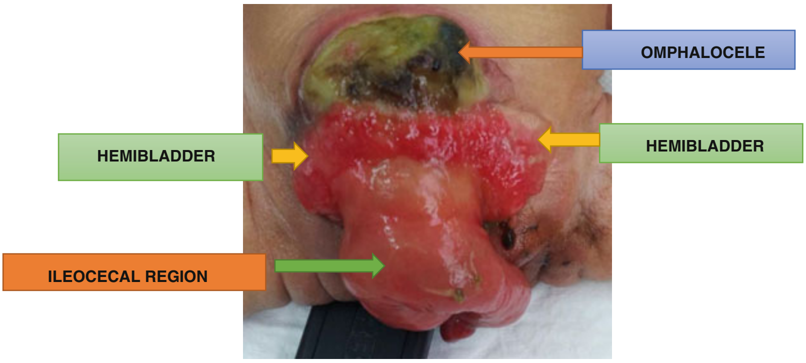

OMPHALOCELE
HEMIBLADDER
HEMIBLADDER
ILEOCECAL REGION

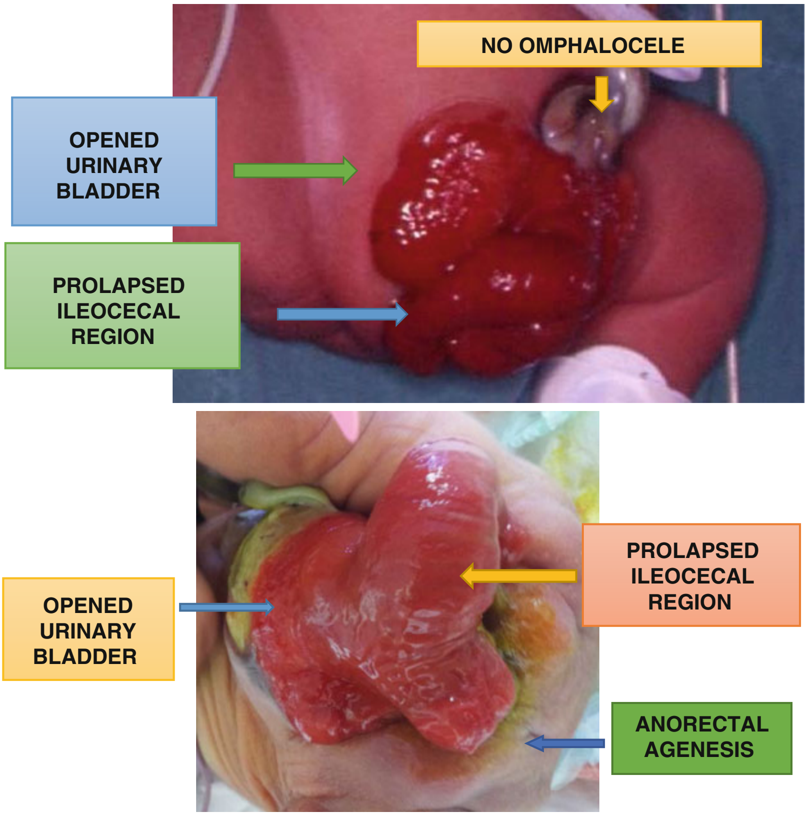
Fig. 18.1 Clinical photograph showing the components of the cloacal exstrophy


OMPHALOCEL
HEMIBLADDER
HEMIBLADDER
ILEOCECAL REGION


OMPHALOCELE
HEMIBLADDER
HEMIBLADDER
ILEOCECAL REGION

Figs. 18.2 and 18.3 Clinical photographs showing two patients with cloacal exstrophy. Note the difference in the size of omphalocele and also the extent of the exstrophied ileo-cecal region

- Embryo logically:
  - The urorectal septum divides the cloaca into an anterior urogenital sinus and a posterior anorectal canal.
  - This occurs around the fourth week of intrauterine life and simultaneously, the cloacal membrane is invaded by lateral mesodermal folds.
  - It is postulated that if this mesodermal invasion does not occur, the infraumbilical cloacal membrane persists leading to poor lower abdominal wall development.
  - The cloacal membrane eventually ruptures but if this happens prior to the descent of the urorectal septum which happens at 6–8 weeks of gestation, then cloacal exstrophy results.
  - Cloacal exstrophy develops as a result of:
    - Failure of the urorectal septum to develop and divides the urogenital sinus anteriorly from the rectum posteriorly.


NO OMPHALOCELE
OPENED URINARY BLADDER
PROLAPSED ILEOCECAL REGION
PROLAPSED ILEOCECAL REGION
OPENED URINARY BLADDER
ANORECTAL AGENESIS

Figs. 18.4 and 18.5 Clinical photographs showing cloacal exstrophy in two patients. Note the absence of omphalocele in the first one and associated anorectal agenesis in the second one

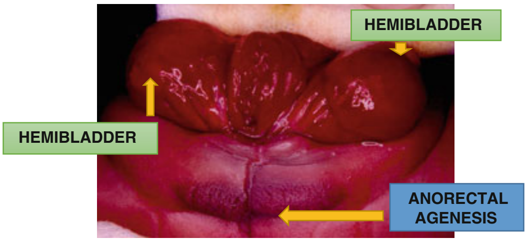

HEMIBLADDER
HEMIBLADDER
ANORECTAL AGENESIS

Fig. 18.6 A clinical photograph showing cloacal exstrophy. Note the associated anorectal agenesis

- Failure of the mesoderm forming the infraumbilical abdominal wall to proliferate and form the lower abdominal wall
- Failure of the genital tubercle to develop.
- Failure of these events to occur results in exstrophy of both bladder and intestine.
  - Classically, cloacal exstrophy is made up of omphalocele, exstrophied ileocecal region of bowel, exstrophied hemi bladders each with its ipsilateral ureter, and anorectal agenesis.
  - The pubic bones are widely separated, and spinal dysraphism is common in these patients.

18.3 Associated Anomalies

- Cloacal exstrophy is commonly associated with other anomalies including cardiovascular, and central nervous system anomalies.
- Omphalocele is present in 70–90 % of patients with cloacal exstrophy.
- Spinal and skeletal anomalies (46 %). These include (Figs. 18.7 and 18.8):
  - Hemivertebra
  - Myelomeningocele
  - Clubfoot deformities
  - Absence of feet
  - Tibial/fibular deformities
  - Hip dislocation

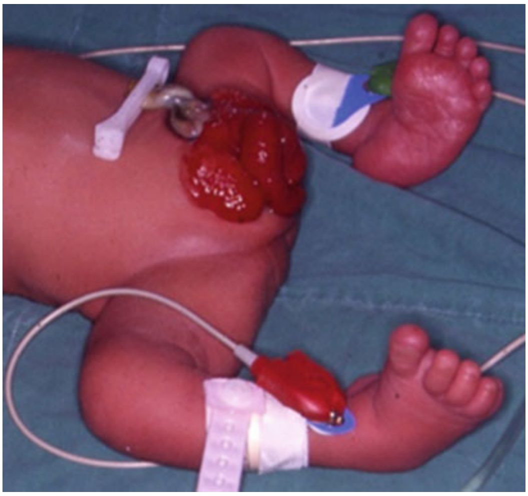


Fig. 18.7 Clinical photograph of a newborn with cloacal exstrophy. Note also the associated bilateral tallipes equinovarus

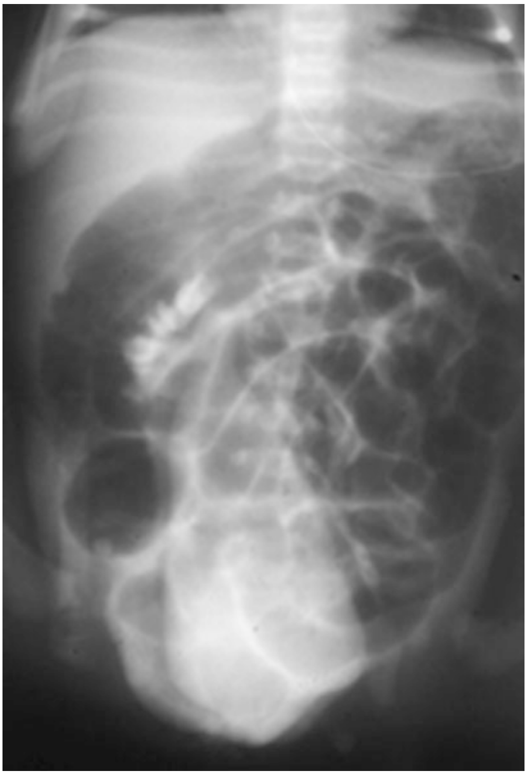


Fig. 18.8 Abdominal x-ray showing widened pubic bone and abnormal asymmetrical pelvis

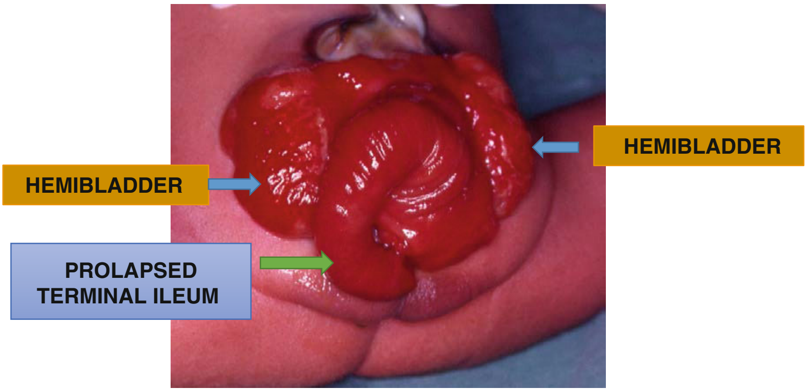
  - Sacralization of L5
  - Congenital scoliosis
  - Sacral agenesis
  - Interpedicular widening

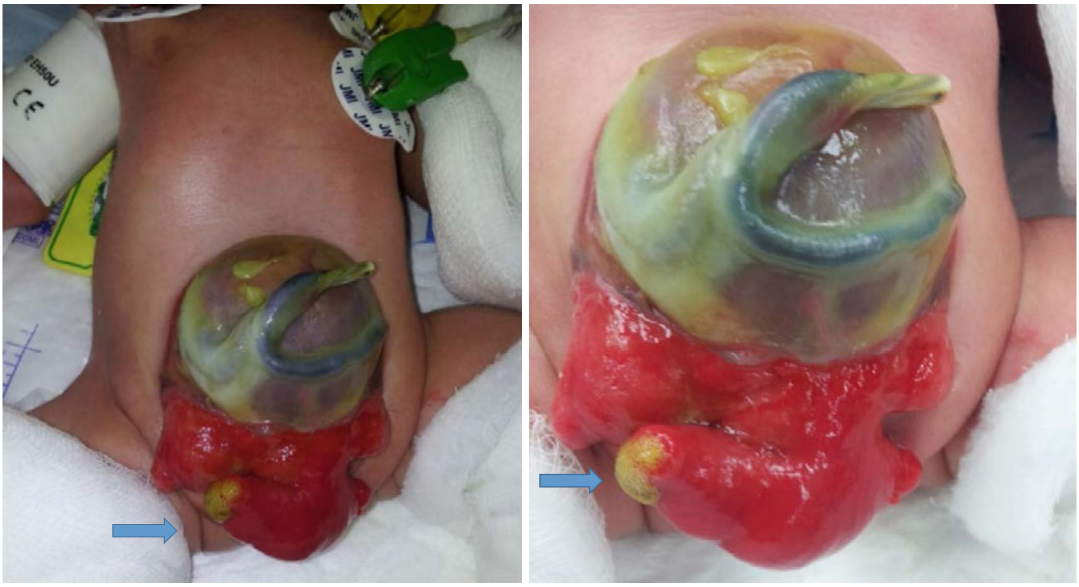
- Upper urinary tract anomalies (42 %).
  - Pelvic kidney
  - Horseshoe kidney
  - Hypoplastic kidney
  - Solitary kidney
- Malrotation (30 %)
  - Urological malformations:
    - Ureteropelvic junction obstruction
    - Ectopic pelvic kidney
    - Horseshoe kidney
    - Hypoplastic kidney or renal agenesis
    - Megaureter
    - Ureteral ectopy and ureterocele
- Lower extremity anomalies (30 %)
- Double appendix (30 %)
- Absent appendix (21 %)
- Short bowel syndrome (19–46 %)
- Gastrointestinal duplications
- Small bowel atresia (5 %)
- Abdominal wall musculature deficiency (1 %)

18.4 Clinical Features and Management

- Cloacal exstrophy is a very rare and complex anomaly of the urogenital tract and intestinal tract resulting in exstrophy of both bowel and bladder (Fig. 18.9).
- Commonly in cloacal exstrophy, the exstrophied bowel is the ileo-cecal region with little or no large bowel distally, but there are cases where there is colonic exstrophy with sufficient large bowel length. A small colon usually ends blindly in the pelvis, and the terminal ileum often prolapses out of the exposed cecum (Figs. 18.10 and 18.11).
- The presence of enough large bowel is advantageous from the reconstruction point of view.
- The extrophied ileo-cecal region and in the presence of short large bowel should be preserved for reconstruction of the anorectal malformation.
- Every effort should be made to preserve all large intestines because not only it can be used for bladder augmentation which is necessary in the majority of these patients to increase the bladder compliance, but also for reconstruction of the anorectal malformation and vaginal reconstruction in those who have vaginal

Fig. 18.9 A clinical photograph showing cloacal exstrophy. Note the prolapsing terminal ileum out of the exposed cecum

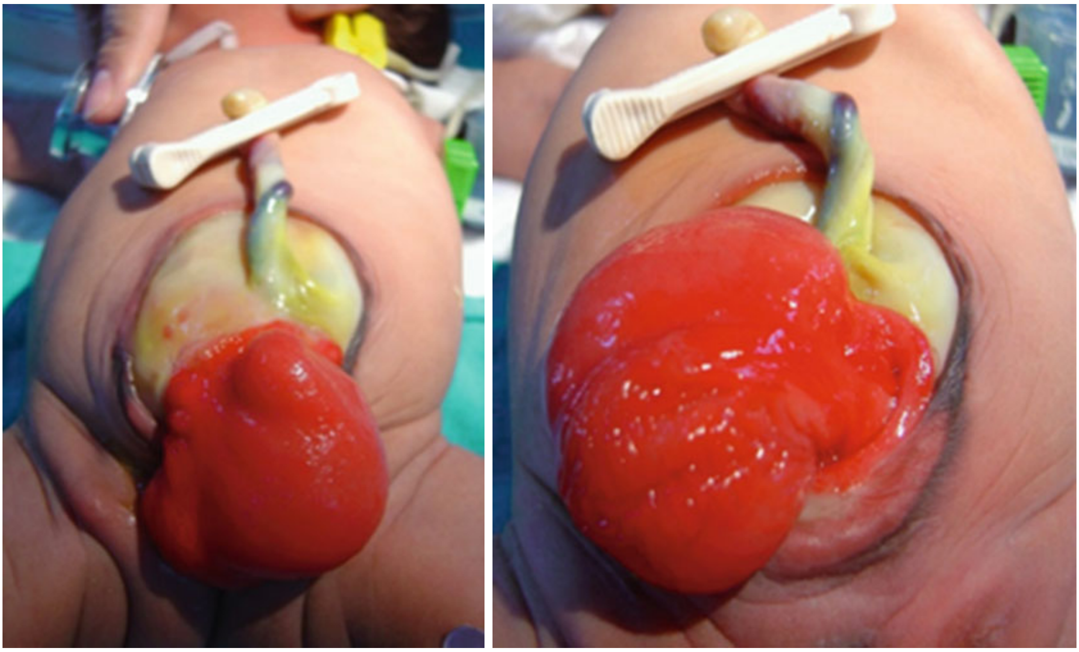




Figs. 18.10 and 18.11 A clinical photograph showing cloacal exstrophy. Note the omphalocele, the urinary bladder into two halves and the prolapsed ileo-cecal region with the terminal ileum open with meconium passing from it. Note the large size of the associated omphalocele

agenesis or those undergoing gender reassignment (Figs. 18.12, 18.13, 18.14, and 18.15).

- Add to this the valuable absorptive function of the large bowel.
- Augmentation of the urinary bladder may be performed using the hindgut if enough length is available, ileum, or part of the stomach. In the absence of large intestine, both small bowel and stomach can be used for bladder augmentation but gastrocytoplasty was shown to be superior.
- Gender assignment is one of the difficult tasks in the management of newborns with cloacal exstrophy.
- Genetic females should not raise a problem as they will be raised as females.
- In genetic males with cloacal exstrophy, the phallic structures are usually small and completely bifid with insufficient phallic tissue to reconstruct an adequate penis.
- There is now general consensus that genetic males with insufficient phallus be gender reassigned as phenotypic females, and to minimize testosterone imprinting on the nervous system, this should be done in the immediate newborn period with early orchidectomy.
- Males with adequate bilateral or unilateral phallic structures should however, be raised as males.
- In the classic repair of cloacal exstrophy in males an epispadias is created initially after



Figs. 18.12 and 18.13 Clinical photographs showing cloacal extrophy. Note the prolapsed bowel and also the abdominal wall defect but no clear omphlocele. The bladder defect is covered by the large prolapsing bowel

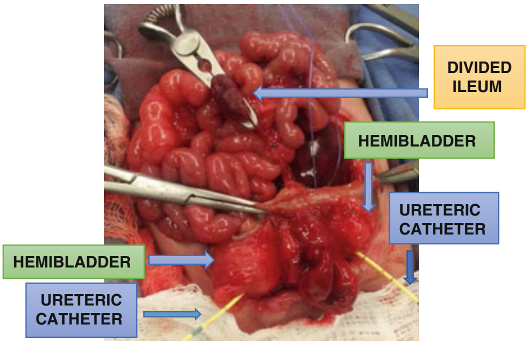


Fig. 18.14 A clinical intraoperative photograph of cloacal exstrophy being repaired. Note the two ureteric catheters inserted and the mobilized urinary bladder. Note also the divided ileum to form an ileostomy. Part of the bowel is left in the posterior wall of the urinary bladder for bladder augmentation

urinary bladder closure. This is repaired later and will require the use of long acting testosterone to increase the size and length of the penis.

- The management of newborns with cloacal exstrophy has progressed over the years, and now a very reasonable outcome is expected in most cases.

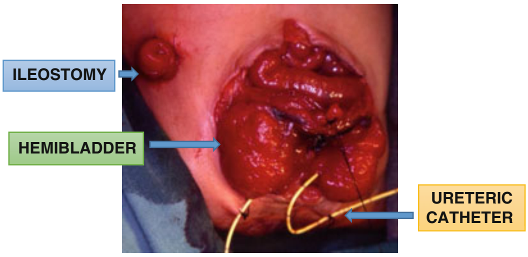


Fig. 18.15 Clinical intraoperative photograph showing a diverting ileostomy and ureteric catheters prior to closure of the urinary bladder

- This, however, requires a team approach including:
  - Neonatologists
  - Pediatric surgeons
  - Pediatric urologist
  - Neurosurgeons
  - Pediatric orthopedic surgeons
  - Geneticists
  - Social workers
  - Stomatherapist
- Although there are general guidelines in managing newborns with cloacal exstrophy, after thor-

ough evaluation of the anatomical abnormalities, the management should be individualized.

- Immediate management is directed to the medical stabilization of the infant.
- Evaluation and appropriate management of associated malformations should be undertaken.
- For infants who have few other associated malformations and are medically stable, staged closure can be considered.
- The bowel should be moistened with saline and covered with protective plastic dressing.
- Evaluation of the genitalia and gender assignment should be made by a gender assignment team, including a pediatric urologist, pediatric surgeon, pediatrician, and pediatric endocrinologist.
- Consultation of social worker, pediatric orthopedic surgeon and other disciplines should be obtained.
- The initial operation consists of:
  - Separating the bowel from the bladder to create an intestinal stoma.
  - Closing the omphalocele.
  - Reapproximating, closing, or leaving the exstrophied bladder undisturbed.
- The importance of creating a colostomy instead of an ileostomy is to be emphasized. This is to prevent problems with diarrhea, dehydration, and acidosis. An ileostomy in these patients will lead to failure to thrive and sever skin excoriations.

Further Reading

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19 Posterior Urethral Valve

19.1 Introduction

- Posterior urethral valve (PUV) disorder is an obstructive developmental anomaly of the male urethra.
- It is characterized by a congenital membrane obstructing the posterior male urethra.
- As a result of urinary obstruction, there is a backward pressure and reverse urinary flow which can affect the urethra, bladder, ureters, and kidneys (Fig. 19.1).
- Hugh Hampton Young published the first description of posterior urethral valves (PUVs) in 1919.
- PUVs occur exclusively in males. The homolog to the male verumontanum from which the valves originate is the female hymen.
- It is considered the most common cause of bladder outlet obstruction in male newborns.
- The incidence of posterior urethra is 1 in 5,000–8,000 live male newborns.
- The valve is believed to result from abnormal embryologic development of the fetal posterior urethra.
- PUV mechanically obstruct normal bladder emptying and increases voiding pressures.
- The disorder varies in degree of obstruction from mild to severe incompatible with postnatal life.
- Severe posterior urethral valves are known to be associated with renal and respiratory failure from lung underdevelopment as result of low amniotic fluid volumes.
- An increasing number of cases are diagnosed antenatally.
- Patients with PUVs have a higher incidence of cryptorchidism when compared to normal patients.
- Other known associated anomalies include VATER or VACTERL and rarely ano-rectal malformation.
- Prenatal intervention in those with PUV does not appear to confer a benefit in the long-term outcome of renal function.
- Primary valve ablation is the recommended treatment of choice with diversion being reserved for specific individual cases.
- The most life-threatening problem in the newborn period is the potential pulmonary hypoplasia related to in utero oligohydramnios and renal dysfunction. These patients may present with pneumothoraces at birth which will complicate their pulmonary management.
- Newborns are also susceptible to urosepsis as a result of urinary stasis.
- The presentation of PUV is variable depending on the degree of obstruction and the spectrum of renal dysfunction and subsequent functional outcomes also vary widely.
- A significant number of boys with PUV will develop chronic kidney disease and end stage renal failure.
- This is attributed to its consequences, including:
  - Renal dysplasia
  - Upper urinary tract dilatation

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A.H. Al-Salem, *An Illustrated Guide to Pediatric Urology*, DOI 10.1007/978-3-319-44182-5_19

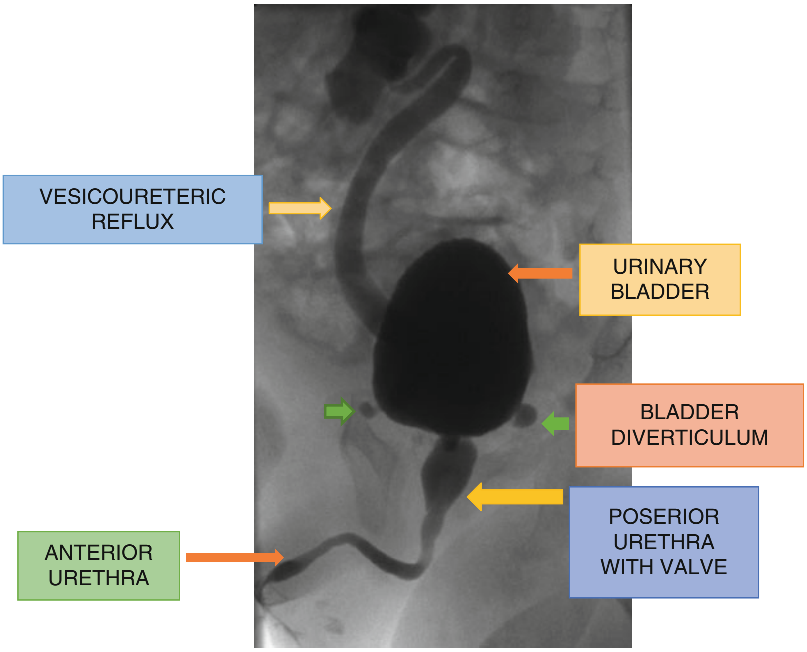


Fig. 19.1 A voiding cystourethrogram showing posterior urethral valve. Note the dilated posterior urethra with the valve, the associated bladder diverticulum and right side vesicoureteric reflux

  - Vesico-ureteric reflux
  - Urinary tract infection
  - Bladder dysfunction
- PUV accounts for 25–30 % of pediatric renal transplantations.
- The VURD (valves unilateral reflux dysplasia) syndrome:
  - This was described by Hoover and Duckett.
  - It results in very poor or non-function of the kidney on the refluxing side with a relative sparing of renal function on the contralateral, non-refluxing side.
  - The authors also postulated that this mechanism of 'pop-off' results in long-term normal renal function, as the contralateral kidney is spared and normal.
  - This hypothesis was subsequently challenged by Cuckow et al. who showed with serum creatinine and GFR measurements that renal function was impaired in cases with VURD, implying that the protection offered by the 'pop-off' mechanism was not complete

19.2 Embryology

- Embryologically, the most caudal end of the Wolffian duct is absorbed into the primitive cloaca at the site of the future verumontanum in the posterior urethra.
- In healthy males, the remnants of this process are the posterior urethral folds, called plicae colliculi.
- The embryological abnormality giving rise to posterior urethral valves is not well known.
- It has been suggested that posterior urethral valves result from fusion of the *plicae colliculi* (posterior urethral folds) between the entrances of the seminal vesicles at the veromontanum, and extend to the membranous urethra.
- PUVs are formed at approximately 4 weeks' gestation, as the Wolffian duct fuses with the developing cloaca.
- There are several theories explaining the embryological origin of PUVs:
  - PUVs may represent an anomalous insertion of the mesonephric duct into the

  uro-genital sinus, preventing normal migration of these ducts and their anterior fusion.
  - PUVs may represent an abnormality of the cloacal membrane.
- Early classification of PUV was done by Hugh Hampton Young in 1919, who described three types of PUVs, I–III based on post-mortem dissection studies.
- Subsequently, Dewan et al. suggested a more uniform and similar appearance to the obstructing posterior urethral membrane.
- Their endoscopic appraisal revealed the membrane to attach posteriorly, just distal to the verumontanum. The membrane extended anteriorly and obliquely beyond the external sphincter with a variable sized aperture located within it, at the level of the verumontanum.
- They described the membrane as congenital obstructing posterior urethral membrane (COPUM).
- Congenital obstructing posterior urethral membrane (COPUM) was first proposed by Dewan and Goh and was later supported by histological studies by Baskin.
- This concept proposes that, instead of a true valve, a persistent oblique membrane is ruptured by initial catheter placement and, secondary to rupture, forms a valve like configuration.

19.3 Pathophysiology

- Posterior urethral valve is known to be associated with significant morbidity which is not merely limited to transient urethral obstruction.
- The congenital obstruction of the urinary tract at a critical time in organogenesis may profoundly affect lifelong kidney, ureteral, and bladder function as follows:
  - Outflow obstruction leads to increased collagen deposition and muscle hypertrophy of the urinary bladder which can significantly thicken the bladder wall.
  - Hypertrophy and hyperplasia of the detrusor muscle of the urinary bladder and increases in connective tissue limit bladder compliance during filling.
  - As a result of this, bladder emptying occurs at high intravesical pressures.
  - This high intravesical pressure, in turn, can be transmitted to the ureters and up into the renal collecting system and kidneys.
  - The end result of this is increased susceptibility to incontinence, infection, and progressive renal damage.
  - The bladder dysfunction may cause ongoing and progressive renal deterioration.
  - Renal insufficiency is caused by PUVs in approximately 10–15 % of children undergoing renal transplantation, and approximately one third of patients born with PUVs progress to end-stage renal disease (ESRD).
- PUVs lead to mechanical obstruction which affect normal bladder emptying and this will lead to:
  - High intraluminal pressure
  - Increases voiding pressures
  - Maldevelopment of the kidneys, ureters and urinary bladder
  - Renal maldevelopment:
    - Renal parenchymal dysplasia is common and may be related to maldevelopment of the metanephric blastema
    - Renal tubular function may be affected by high pressures that result in poor urinary concentrating ability
    - Diuresis secondary to high urinary production
    - This high urinary production will lead to ureteral and bladder dysfunction
  - Renal deterioration may also occur due to hyperfiltration injury that causes:
    - Glomerulosclerosis
    - Chronic pyelonephritis associated with vesicoureteral reflux
    - Urinary stasis
    - Incomplete bladder emptying
  - These will also cause further insult to the developing kidneys.

- Hydronephrosis is common in these patients for several reasons:
  - Bladder dysfunction with high back pressures on the ureter.
  - An abnormally deficient musculature of the ureter due to chronic distention from high pressure or high urine flow.
  - High urinary flow due to the lack of urinary concentrating ability of the nephron can dilate the kidneys and ureters.
  - Abnormalities of the vesicoureteral junction, such as reflux or, rarely, ureterovesical obstruction.
- Vesicoureteral reflux is present in one half of male patients with a posterior urethral valve for the following reasons:
  - Secondary to increased intravesical pressure which overcomes the competence of the ureterovesical junction.
  - Secondary to abnormal ureteral orifice position resulting from abnormal ureteral bud development during embryogenesis.
- Bladder dysfunction in patients with PUV is secondary to:
  - Alterations in collagen deposition.
  - Alteration in the development of detrusor smooth muscle cells.
  - Poor compliance or uninhibited contraction of the detrusor muscle and eventual myogenic failure.
  - In mild cases, incontinence may be present.
  - In severe cases, ongoing deterioration of renal function occurs.
  - Bladder dysfunction often improves over time after definitive treatment of the obstruction.
  - Persistence of bladder dysfunction increases the risk of:
    - Urinary tract infection
    - Persistent hydronephrosis
    - Vesicoureteral reflux
    - Incontinence
  - All of these diminish renal function further.
- Several protective mechanisms may develop in boys with a posterior urethral valve; these may lower intraluminal pressures and allow at least one renal unit to develop more normally. These protective mechanisms include:
  - Massive unilateral vesicoureteral reflux.
  - This is usually associated with an ipsilateral dysplastic kidney, known as vesicoureteral reflux and dysplasia syndrome.
  - Development of bladder diverticula.
  - Rupture of renal calyces and development of urinary ascites.
- As patients with PUV age, bladder decompensation may develop, resulting in detrusor failure and increased bladder capacity.
- Many boys with PUV as they grow older will develop larger-than-expected bladder volumes possibly due to overproduction of urine caused by tubular dysfunction and an inability to concentrate urine (nephrogenic diabetes insipidus).
- Bladder function may change at puberty, resulting in high-pressure, chronic retention and necessitating the need for lifelong bladder management.
- Symptoms of bladder dysfunction may persist into adulthood in up to one third of patients and include urinary incontinence in up to 15 % of adults with a history of PUV.

19.4 Classification

- A PUV is a congenital obstruction caused by an embryological malformation of the posterior urethra.
- Posterior urethral valves are usually fusion of the plicae colliculi between the entrances of the seminal vesicles at the veromontanum, and extend to the membranous urethra.
- The verumontanum, or mountain ridge, is a distinctive landmark in the prostatic urethra and it is important in the classification of posterior valves.
- This malformation will result in urethral obstruction.
- The significance of this obstruction depends on the secondary effects on:
  - The urinary bladder
  - The ureters
  - The kidneys

- In 1919, H. H. Young was the first to classify posterior urethral valves into three types as follows:
  - Type I:
    - This is the most common type.
    - This type of obstruction is believed to result from abnormal insertion and absorption of the most distal aspects of the Wolffian ducts during bladder development.
    - In the healthy male, the remnants of these ducts are observed as the plicae colliculi.
    - This type is believed to be due to anterior fusing of the plicae colliculi, mucosal fins extending from the bottom of the verumontanum distally along the prostatic and membranous urethra.
  - Type II:
    - This is the least common variant.
    - It is characterized by vertical or longitudinal folds between the verumontanum and proximal prostatic urethra and bladder neck.
  - Type III:
    - This is the second common variant.
    - It is due to a disc of tissue distal to verumontanum.
    - These valves are observed as a membrane in the posterior urethra
    - These are believed to originate from incomplete canalization between the anterior and posterior urethra.
    - It is also theorized to be a developmental anomaly of congenital urogenital remnants in the bulbar urethra.
- It has been suggested that obstructions in the posterior urethra are more appropriately termed congenital obstructions of the posterior urethral membrane (COPUMs).
- The congenital urothelial remnants of type III posterior urethral valves have been eponymously referred to as Cobb's collar or Moorman's ring.

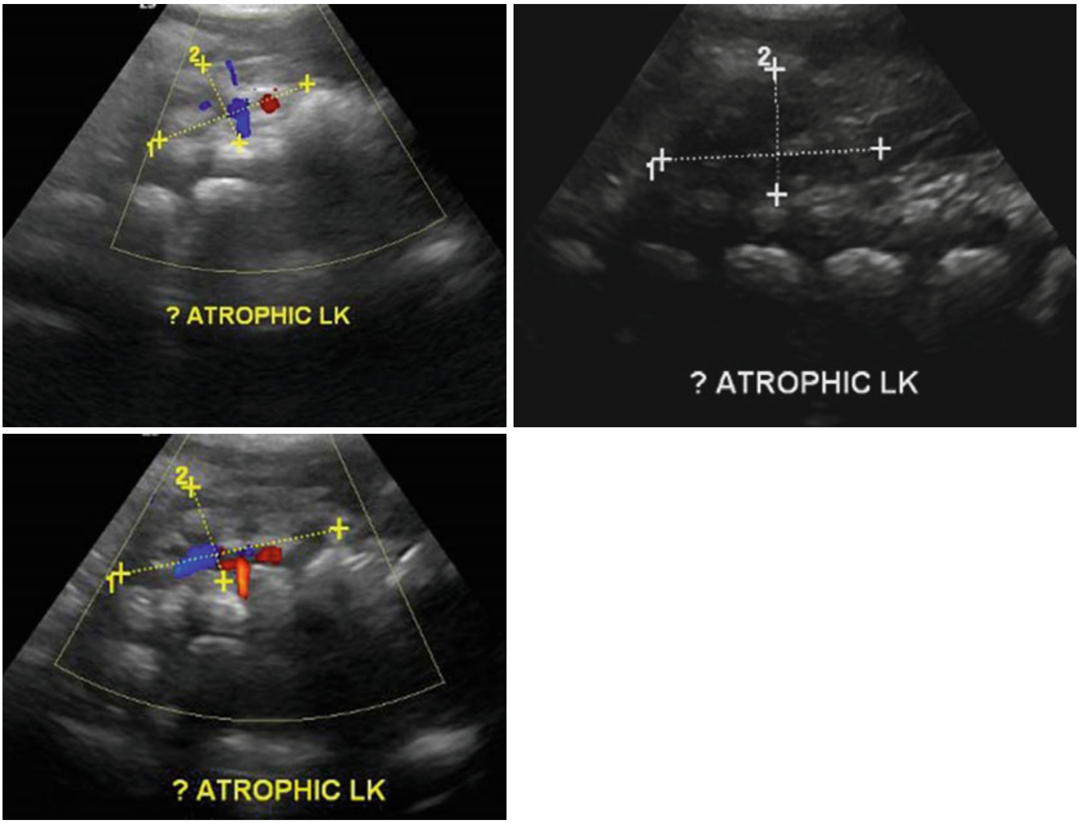
19.5 Clinical Features

- PUV is the most common cause of lower urinary tract obstruction in male neonates.
- The reported incidence is 1 per 8,000–1 per 25,000 live births.
- PUVs are the cause of renal insufficiency in approximately 10–15 % of children undergoing renal transplant.
- Approximately one third of patients born with PUV progress to end stage renal disease (ESRD).
- PUVs are usually diagnosed before birth or at birth when a boy is evaluated for antenatal hydronephrosis.
- Before the era of prenatal ultrasonography, PUVs were discovered during evaluation of urinary tract infection (UTI), voiding dysfunction, or renal failure.
- In the pre-antenatal ultrasonography era, a late presentation of PUV was considered a good prognostic indicator suggestive of a lesser degree of obstruction.
- Prenatal diagnosis
  - The widespread use of antenatal ultrasonography has made it possible to diagnose more cases of posterior urethral valves antenatally.
  - Currently, the diagnosis of PUV is usually made early at birth when a boy is evaluated for antenatally diagnosed hydronephrosis.
  - It was estimated that 10 % of boys diagnosed with prenatal hydronephrosis had PUVs.
  - Patients who are not diagnosed by antenatal ultrasound may present shortly after birth with distended bladder and difficulty to pass urine.
  - Despite widespread use of antenatal ultrasonography, some patients with PUVs do present later in life.
- Delayed presentation
  - PUVs manifest as a spectrum of disease severity.
  - The delayed clinical presentation of PUVs include:
    - Urinary tract infection
    - Diurnal enuresis in boys older than 5 years
    - Secondary diurnal enuresis
    - Voiding pain or dysfunction
    - An abnormal urinary stream

  - PUVs are sometimes discovered during evaluation of abdominal mass or renal failure.
  - Hydronephrosis or proteinuria found on examination for unrelated conditions may be the first sign of PUVs.
- Neonates born with severe posterior urethral valve may present with severe pulmonary distress secondary to pulmonary hypoplasia due to oligohydramnios. Physical findings can include the followings:
  - Poor fetal breathing movements
  - Small chest cavity
  - Abdominal mass (ascites)
  - Potter facies
  - Limb deformities (skin dimpling)
  - Indentation of the knees and elbows due to compression within the uterus
- In older children, physical findings can include:
  - Poor growth
  - Hypertension
  - Lethargy
  - A large lower abdominal mass representing a markedly distended urinary bladder
- A smaller number of patients with PUV will present late and their clinical presentation include:
  - Diurnal enuresis
  - Dribbling or poor urine stream
  - Urinary tract infection
  - Hematuria

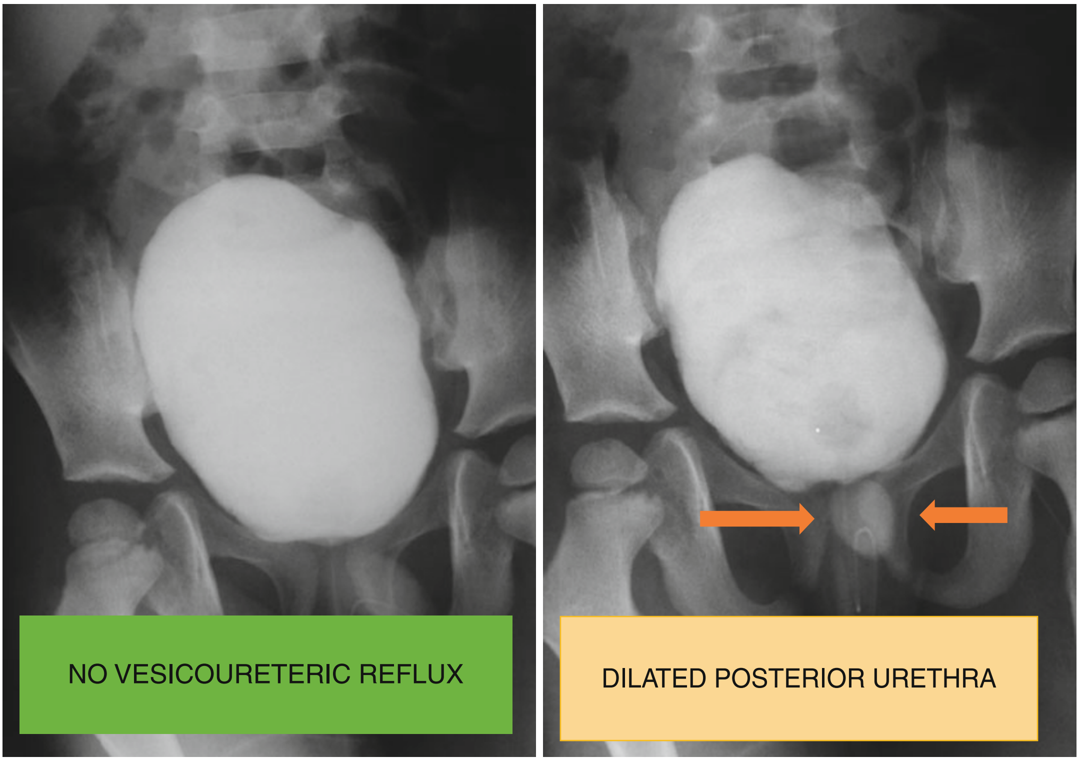
19.6 Investigations and Diagnosis

- With routine use of obstetric ultrasonography the prenatal diagnosis of posterior urethral valve is becoming increasingly common.
- The antenatal ultrasound demonstrates significant hydronephrosis with possible renal cortical thinning. The kidney is larger than expected for the patient's gestational age. The hydronephrosis may be bilateral and both kidneys may be affected.
- As a result of the routine use of antenatal ultrasound, the number of cases of PUV diagnosed prenatally has increased.
- Currently, approximately 50–75 % of boys with PUV will be suspected on prenatal ultrasound.
- The prenatal ultrasound findings suggestive of PUV include:
  - A thick walled bladder
  - The 'keyhole' sign with a dilated bladder and posterior urethra
  - Unilateral or bilateral hydroureteronephrosis
  - Echo bright kidneys
  - Oligohydramnios
- Postnatally, the patient must be stabilized prior to any investigation.
- Complete blood count
- Serum electrolytes, BUN and creatinine.
  - To be accurate and to avoid maternal placental effect, these should be checked at least 24 h after birth.
  - The newborn is unable to concentrate urine because of renal immaturity at birth.
  - This defect is exacerbated by renal dysplasia such as that found with posterior urethral valves and if the renal dysplasia is significant, the serum creatinine fails to reach a normal level during the first year of life.
  - Serum creatinine levels >0.8 mg/dL during the first year of life have been demonstrated to be associated with poor long-term renal function.
  - This is considered a negative prognostic indicator.
- Plain abdominal radiographs do not add to the actual diagnosis of posterior urethral valves but may show the ground-glass appearance seen in those with urinary ascites.
- Chest radiographs may be useful in the evaluation of pulmonary hypoplasia.
- Renal and bladder ultrasonography
  - Postnatal renal ultrasonography is the initial investigation to be done in those with suspected posterior urethral valve.
  - This is important as an initial noninvasive and devoid of radiation investigation.
  - Ultrasonography is helpful but not diagnostic (Figs. 19.2, 19.3, and 19.4).



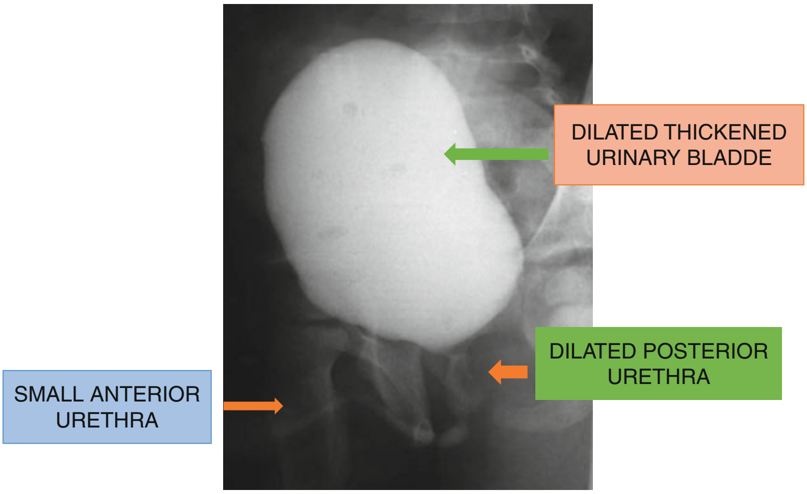
Figs. 19.2, 19.3, and 19.4 Abdominal ultrasound showing an atrophic dysplastic kidney seen in a patient with posterior urethral valve and vesicoureteric reflux

- Features suggestive of posterior urethral valves are:
  - Unilateral or bilateral hydronephrosis
  - Enlarged kidneys with thinning of the renal cortex
  - In those with renal dysplasia, the renal parenchyma is typically hyperechogenic with visible small cysts (<10 mm), but in the most mildly affected cases, renal ultrasonographic findings may be normal.
  - A thickened bladder wall with trabeculations, and bladder diverticula
  - The bladder may be of large or small volume, but it is invariably thick-walled.
  - A dilated posterior urethra
  - Echogenic lines that are the actual valve leaflets might be seen.
  - The combination of the dilated, thick-walled bladder and dilated posterior urethra has been described as having a keyhole appearance.
  - Urinary ascites or perinephric collections due to urinomas may also be seen, most commonly soon after birth, and are caused by rupture of the urinary tract, typically at the level of the calyces.
- Voiding cystourethrogram (VCUG) (Figs. 19.5, 19.6, 19.7, 19.8, 19.9, 19.10, and 19.11):
  - This is more specific for the diagnosis of posterior urethral valve.
  - This should be performed under fluoroscopy, with imaging of the posterior urethra, especially during the voiding phase.
  - PUV on voiding cystourethrogram is characterized by an abrupt tapering of urethral caliber near the verumontanum, with the specific level depending on the developmental variant.


NO VESICOURETERIC REFLUX
DILATED POSTERIOR URETHRA

Figs. 19.5 and 19.6 A micturating cystourethrogram showing posterior urethral valve. Note the dilated posterior urethra. Note also the dilated thickened urinary bladder. Note also the absence of vesicoureteric reflux

Fig. 19.7 A micturating cystourethrogram showing posterior urethral valve. Note the dilated posterior urethra and the small anterior urethra. Note also the dilated thickened urinary bladder


DILATED THICKENED URINARY BLADDE
DILATED POSTERIOR URETHRA
SMALL ANTERIOR URETHRA

- The diagnosis of PUV is indicated by the following features:
    - A thickened trabeculated bladder
    - A dilated or elongated posterior urethra
    - The bladder neck is typically hypertrophic, leading to a lucent ring or collar
    - Visualization of the valve leaflets
    - The posterior urethral valve is seen as a nonopacified line that separates the dilated posterior urethra from the normal-caliber distal urethra
    - The findings of bladder diverticula

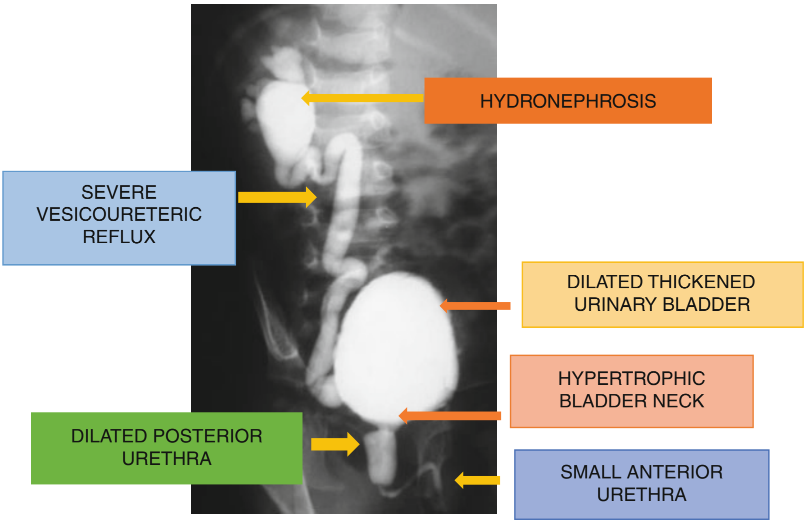

HYDRONEPHROSIS
SEVERE VESICOURETERIC REFLUX
DILATED THICKENED URINARY BLADDER
HYPERTROPHIC BLADDER NECK
DILATED POSTERIOR URETHRA
SMALL ANTERIOR URETHRA

Fig. 19.8 A micturating cystourethrogram showing posterior urethral valve. Note the dilated posterior urethra and the small anterior urethra. Note also the dilated thickened urinary bladder and severe unilateral vesicoureteric reflux

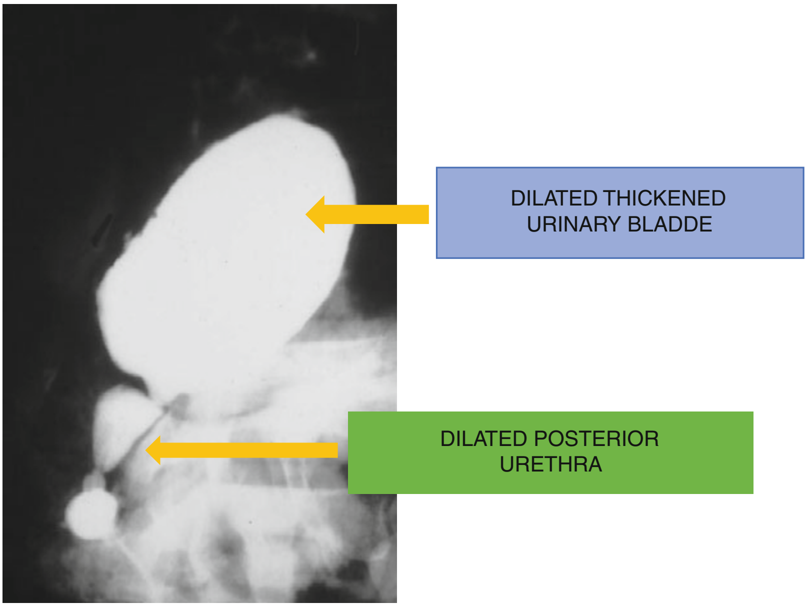

DILATED THICKENED URINARY BLADDE
DILATED POSTERIOR URETHRA

Fig. 19.9 A micturating cystourethrogram showing posterior urethral valve. Note the dilated posterior urethra and the dilated thickened urinary bladder. Note also the absence of vesicoureteric reflux

- Vesicoureteral reflux is also seen in over 50 % of cases. This can be unilateral or bilateral
- Reflux into the ejaculatory ducts secondary to elevated bladder and urethral pressures may also be seen.
- The anterior urethra is typically smaller, under filled, and voiding is incomplete
- If the VUR has been high grade and unilateral, a “pop-off” may have allowed selective dissipation of back pressure, resulting from urethral obstruction.
- Intravenous urography (IVU):
  - IVU is not routinely used in children with posterior urethral valve.
  - The contrast agent is poorly concentrated and visualized in newborn kidneys, particularly if renal function is diminished.
  - Elevated serum creatinine levels may preclude the use of IV contrast material.
  - IVU may show:
    - An absent kidney in the case of renal dysplasia or delayed renal function with persistent high intraluminal pressures.

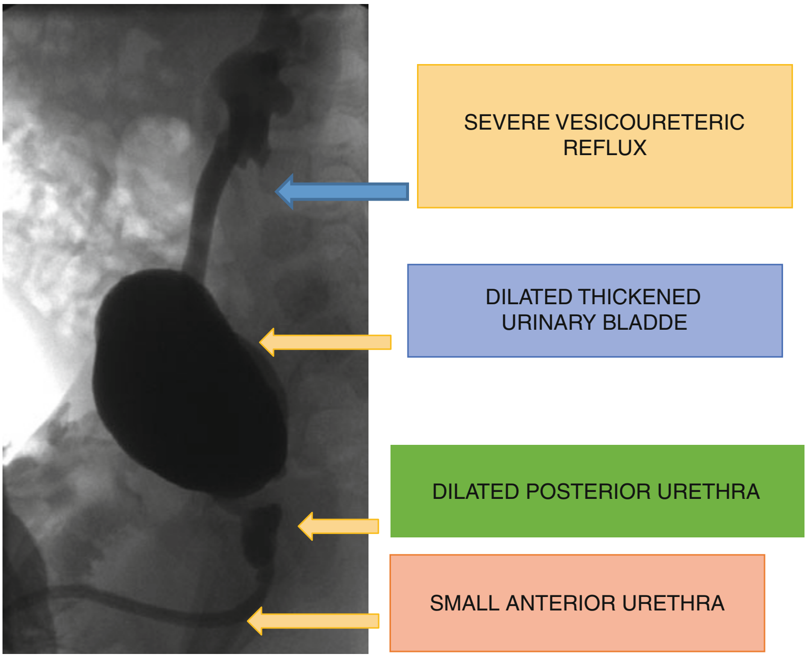
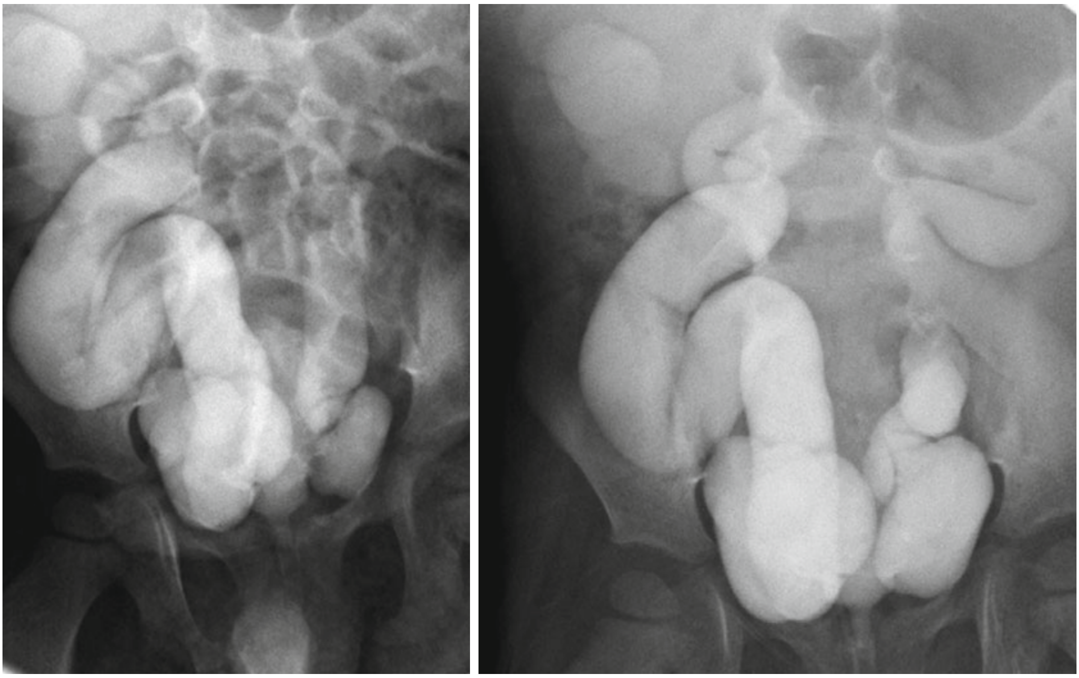

SEVERE VESICOURETERIC REFLUX
DILATED THICKENED URINARY BLADDE
DILATED POSTERIOR URETHRA
SMALL ANTERIOR URETHRA

Fig. 19.10 A micturating cystourethrogram showing posterior urethral valve. Note the dilated posterior urethra and the dilated thickened urinary bladder. Note also the small anterior urethra and unilateral vesicoureteric reflux

    - Hydroureteronephrosis may be seen.
    - Delayed images may show bladder or urethral pathology, but the lower urinary tract is better visualized with VCUG.
- Computed Tomography:
  – This is rarely necessary for the diagnosis of posterior urethral valves.
  – Elevated serum creatinine levels generally preclude use of IV contrast material.
  – CT scans with IV contrast enhancement may reveal:
    - Dysplastic and/or dilated kidneys
    - Delayed renal function and excretion
    - Hydroureter
    - Dilated bladder with wall thickening, trabeculation, and diverticula
    - A dilated posterior urethra might be seen
- Magnetic Resonance Imaging:
  – Magnetic resonance imaging (MRI) is rarely used to diagnose posterior urethral valve
  – The findings are similar to those of CT scanning
  – Gadolinium-based contrast agents used in MRI have been linked to the development of nephrogenic systemic fibrosis (NSF) or nephrogenic fibrosing dermopathy (NFD).
  – The disease has occurred in patients with moderate to end-stage renal disease after being given a gadolinium-based contrast agent to enhance MRI or MRA scans.
  – NSF/NFD is characterized by:
    - Red or dark patches on the skin
    - Burning, itching, swelling, hardening, and tightening of the skin
    - Yellow spots on the whites of the eyes
    - Joint stiffness with trouble moving or straightening the arms, hands, legs, or feet
    - Pain deep in the hip bones or ribs
    - Muscle weakness
    - Sometimes it is fatal
- Nuclear Imaging:
  – Nuclear cystography is useful to define the presence of vesicoureteral reflux but it is not useful to define the extent or degree of reflux.
  – Renal scintigraphy can determine the relative renal function.
  – The bladder should be drained prior to the study to eliminate the effect of a distended, high-pressure bladder on renal function and drainage.
  – The presence of a much thickened hypertrophied bladder wall may lead to secondary ureterovesical junction obstruction.



Figs. 19.11 and 19.12 Micturating cystourethrograms showing severe bilateral reflux

  - Tc-dimercaptosuccinic acid (DMSA), glucoheptonate, and mercaptoacetyltriglycine (MAG-3) renal scintigraphy provide information about relative renal function.
  - The presence of photopenic areas within the kidney indicate scarring or dysplasia.
  - An absent or dysplastic kidney is seen as a photopenic area in the renal fossa
  - The MAG-3 renal scan with furosemide (Lasix) provides information about renal drainage and possible obstruction.
- Urodynamic studies:
  - These provide information about bladder storage and emptying.
  - The term "valve bladder" is used to describe patients with PUV and a fibrotic noncompliant bladder. These patients are at risk of developing:
    - Hydroureteronephrosis
    - Progressive renal deterioration
    - Recurrent infections
    - Urinary incontinence
  - Patients with PUV require periodic urodynamic testing throughout childhood because bladder compliance may further deteriorate over time.
- Cystourethroscopy may be required to formally confirm the diagnosis of posterior urethral valves at the time of intervention (Fig. 19.12).

19.7 Management

- The management of patients with posterior urethral valve requires a multidisciplinary team including:
  - Pediatric urologists
  - Pediatric pulmonologists
  - A general pediatrician
  - Pediatric nephrologist
  - Neonatologists
  - Radiologists
  - The family
- The aims should be:
  - To treat pulmonary distress if present
  - To relief urethral obstruction by passing a small size 5 F feeding tube
  - Fluid and electrolytes management
  - Valve disruption
  - Treatment of bladder dysfunction and renal insufficiency

- Treatment of the lower urinary tract may influence progression of upper tract disease.
- Few patients with PUV present with bilateral renal dysplasia at birth. Currently, these patients can be treated successfully with peritoneal dialysis and subsequently at around 1 year of age with renal transplantation.
- Approximately one third of patients with PUV progress to ESRD and these patients are treated with dialysis and subsequently renal transplantation.
- Growth in these children may be significantly retarded and below the reference range for the child's age.
- These patients should have a balanced caloric and protein intake to avoid an accelerated rise in serum creatinine levels.
- Renal dysfunction and progression of ESRD can be accelerated by:
  - Increased metabolic workload on the kidneys as seen at puberty
  - Recurrent infections
  - Elevated bladder pressures
  - Increased caloric and protein intake
- Prenatal Intervention:
  - There remains no clinical consensus about the efficacy and use of prenatal intervention.
  - It was shown that there is a link between urine outflow impairment and renal dysplasia.
  - Lung hypoplasia is seen in patients with PUVs in association with oligohydramnios.
  - Currently, it is difficult to identify fetuses with PUVs who may benefit from prenatal intervention.
  - At the present time, there is no single marker or combination of fetal urine markers that is reliable in identifying fetuses with PUVs who may benefit from prenatal intervention.
  - Gestational age at diagnosis (<24 weeks) and oligohydramnios have been found to be significant predictors of a worse renal outcome.
  - The aim of prenatal intervention in those with PUVs is to decompress the fetal renal tract.
  - This limit the associated lung underdevelopment, or pulmonary hypoplasia, that is seen at birth in these patients.
  - Fetal surgery is a high risk procedure reserved for cases with severe oligohydramnios.
  - This will allow:
    - Improved survival
    - Preservation of renal function
    - Reduction in the respiratory compromise and limb abnormalities seen in association with severe oligohydramnios.
  - The specific procedures for in utero intervention include:
    - Infusions of amniotic fluid
    - Serial bladder aspiration (Serial vesicocentesis)
    - A vesicoamniotic shunt.
  - The risks of fetal surgery are significant and include limb entrapment, abdominal injury, and fetal or maternal death.
- Treatment of posterior urethral valve is by endoscopic valve ablation.
- There are three specific endoscopic treatments of posterior urethral valves:
  - Vesicostomy followed by valve ablation.
  - Pyelostomy followed by valve ablation.
  - Primary (transurethral) valve ablation.
- Currently, the standard treatment of posterior urethral valve is primary (transurethral) ablation of the valves.
- Urinary diversion is rarely used and only used in selected cases.
- Postoperatively, patients with posterior urethral valve should have regular and long term follow-up.
- Neonatal Management:
  - A size 6 Fr urethral catheter or feeding tube should be passed to drain the bladder and antibiotic prophylaxis should be started (e.g. trimethoprim 2 mg/kg).
  - In those neonates where it is not possible to pass a catheter, a supra-pubic catheter should be inserted.
  - These patients should be followed up closely including urine output and electrolyte measurements.
  - These patients may develop polyuria and/or abnormalities of sodium, potassium and bicarbonate as a result of excessive renal losses secondary to post-obstructive diuresis.

  - Creatinine level should be monitored daily till they normalize.
  - In boys born with a history of oligohydramnios and significant pulmonary hypoplasia the priority of management is respiratory support and bladder drainage. Either a urethral or supra-pubic catheter is sufficient to optimize urinary drainage whilst awaiting respiratory stability.
  - Neonates and infants who were not suspected to have PUV prenatally may present with:
    - Urosepsis
    - Obstructive voiding symptoms
    - A distended bladder
    - Palpable kidneys
- Primary Valve Resection:
  - The procedure of choice for PUV is primary valve ablation.
  - This should be performed once the baby is stable.
  - The patient should be covered with antibiotics.
  - A diagnostic cystoscopy using 0° 6/8 Fr neonatal cystoscope is performed.
  - The diagnosis of PUV is confirmed.
  - The configuration of the bladder neck and appearances of the bladder and ureteric orifices should also be noted.
  - A resectoscope is used to resect the valve with either the cold/sickle blade or bugbee electrode.
  - Valve resection is typically performed at the 5, 7 and 12 o'clock positions.
  - A urethral catheter is placed at the end of the procedure and removed 24–48 h later.
  - Complications of primary valve ablation include:
    - Bleeding
    - Incomplete valve resection
    - Urethral stricture
    - Inadvertent damage to the external sphincter
  - For preterm or very small neonates, endoscopic resection is delayed due to the difficulties of the small caliber of the urethra and potential complications of using the relatively larger instruments.
  - These children may be managed with a transurethral or supra-pubic catheter until such time as they are big enough for the procedure.
  - As a guide, a body weight of 2.5 kg should allow safe and accurate PUV resection with standard endoscopic instruments.
  - An alternative technique for small neonates and to avoid the complications associated with urethral or suprapubic catheters, a vesicostomy is constructed to ensure adequate and continuous bladder drainage.
  - It is recommended that all boys have a follow-up cystoscopy within 3 months of the primary procedure to ensure completeness of valve ablation.
  - Others advocate a repeat MCUG within 3 months of the primary procedure and proceed to cystoscopy only if the MCUG suggests persisting urethral obstruction.
- Cystoscopy:
  - Cystoscopy is important to confirm the diagnosis of PUV
  - Therapeutic cystoscopy (i.e., transurethral incision of the PUVs):
    - Multiple techniques have been described for ablating the valves.
    - Currently, PUVs are disrupted under direct vision by cystoscopy using an endoscopic loop, Bugbee electrocauterization, or laser fulguration.
    - In extremely small infants (<2,000 g), a 2 F Fogarty catheter may be passed either under fluoroscopic or direct vision for valve disruption.
    - It is important to perform valve disruption in the least traumatic way to avoid secondary urethral stricture or injury to the urethral sphincter mechanism.
    - A temporary vesicostomy may be performed in small infants with small urethra that does not admit available cystoscopic instruments.
- Bladder management:
  - Place a 5 F or 6 F urethral catheter to allow for bladder drainage.
  - Cystoscopic valve fulguration can be performed within the first few days of life.

  - A vesicostomy can be performed as a temporary solution in those with a small urethra that can not accommodate the instrument.
  - Cutaneous ureterostomies are rarely performed and reserved for those with secondary ureterovesical junction obstruction from bladder hypertrophy.
  - Severe or prolonged urethral obstruction can lead to a fibrotic, poorly compliant bladder. This is secondary to increased bladder collagen deposition and detrusor muscle hypertrophy and hyperplasia. This will led to:
    - Poor compliance of the urinary bladder
    - Elevated urinary bladder storage pressures
    - Increased risk of vesicoureteric reflux
    - Increased risk for hydroureteronephrosis
    - Increased risk of urinary incontinence
  - The use of urodynamic testing to assess bladder compliance help identify patients at risk.
  - Some of these patients may respond to anticholinergic medication, such as oxybutynin.
  - The use of clean intermittent catheterization (CIC) may help some of these patients to achieve continence by preventing the bladder from overfilling.
  - In patients who do not gain adequate bladder capacity and safe compliance despite optimal medical management, augmentation cystoplasty may be required.
- Surgical treatment:
  - The surgical treatment of patients with PUVs varies according to age, bladder status, and renal status.
  - Prenatal surgery has been reported in patients diagnosed with PUV with the goal of improving postnatal outcomes.
  - Antenatal intervention with vesicoamniotic shunting would improve postnatal renal function.
  - However, identification of those patients who may benefit from this early intervention remains unclear and because of this prenatal intervention remains limited.
  - Postnatal primary valve ablation:
    - Transurethral incision of the PUV during the first few days of life is the preferred treatment.
    - The valves can be incised at the 12-, 5-, and 7-o'clock positions, with either a cold knife or electrocautery.
    - Some surgeons prefer to leave a catheter in place for 2–3 days after the procedure.
    - Approximately two thirds of patients have successful valve ablation with one procedure.
    - One third of patients require a second incision.
    - Because approximately one third of patients will require a second valve incision, some authors recommend routine surveillance cystoscopy 1–2 months after initial incision to evaluate and treat any residual valve.
    - The timing of the postoperative VCUG varies and ranges from several days to several months.
  - Vesicostomy:
    - This is reserved for patients with small urethral size that cannot accommodated the available instruments.
    - This allows free bladder drainage.
    - It is important to create an adequate stoma as a large vesicostomy may be complicated by bladder prolapse while a small stoma may result in stomal stenosis and inadequate bladder emptying.
  - Cutaneous ureterostomies:
    - Bilateral cutaneous ureterostomies can be performed to provide for urinary drainage.
    - Techniques for cutaneous ureterostomy include:
      - End stomal ureterostomy
      - Loop ureterostomy
      - Y-ureterostomy (in which the ureter is divided and one end is brought to the skin and the other is reanastomosed in a uretero-ureterostomy)
      - Ring ureterostomy

    - Potential complications of cutaneous ureterostomies include:
      - Ureteral devascularization
      - Inadequate drainage
      - Stomal stenosis
- Secondary bladder surgery:
  - Augmentation cystoplasty:
    - Indications for bladder augmentation include:
      - Inadequately low bladder storage volumes and high bladder pressures despite anticholinergic medication and clean intermittent catheterization.
  - Augmentation cystoplasty can significantly improve patient lifestyle in those who have intractable incontinence due to poor compliance and bladder overactivity.
  - By lowering intravesical pressures, the upper urinary tract may also be protected.
  - The ileum is most commonly used; however, large bowel, stomach, and ureter are also used.
  - Augmentation should only be offered to patients willing to commit to lifelong intermittent catheterization.
  - Potential complications include:
    - Bladder rupture (approximately 10 % of patients)
    - Electrolyte disturbances, which may be worsened by the placement of intestinal mucosa in contact with urine, especially in those with a serum creatinine greater than 2 mg/dL.
    - Mucus production, which can be a source of catheter blockage and may be a nidus for stone formation.
    - The future risk of neoplasia has not yet been defined in these patients, but several cases of malignant degeneration in augmented bladder have been reported.
  - Continent appendicovesicostomy:
    - In children with PUVs, institution of clean intermittent catheterization through the sensitive urethra can be difficult.
    - In addition, some patients may have a much dilated proximal urethra which may not be easily catheterized.
    - The procedure involves placement of a nonrefluxing tubular conduit for catheterization between the bladder and skin to provide an alternative channel for catheterization.
    - This is also called the Mitrofanoff technique
    - The catheterizable tubular conduit can be formed from:
      - The appendix
      - The ureter
      - Tubularized bowel
    - The stoma often can be hidden in the umbilicus to provide acceptable cosmesis.
- Some patients with PUV:
  - Continue to suffer from urinary tract infection
  - Their renal function remains fragile or deteriorates
  - Have a significant deterioration in the appearance of the upper tracts
  - Their bladder emptying is incomplete
- The aim in these children should be to maximize their renal potential and to delay or avoid renal replacement.
- These patients can be managed by early urinary diversion, either by vesicostomy or bilateral ureterostomy or pyelostomy. This aims to protect the upper urinary tracts and minimize the risks of infection.
- A recent development is the use of a refluxing ureterostomy as a form of urinary diversion. The refluxing ureterostomy is particularly useful in boys with fragile renal function. This technique will minimize the potential harmful effects of the high-pressure bladder that is present in the early period following valve ablation.

19.8 Medications Used in Patients with PUV

- The primary medications involved in bladder management are anticholinergic medications used to improve bladder compliance.

- Other medications that may be needed include prophylactic antibiotics and medications used in the management of renal insufficiency.
  - Anticholinergic medications are used to improve bladder capacity and compliance in the patient with elevated detrusor pressures, which may cause hydronephrosis, UTI, or incontinence.
  - Early use of anticholinergic medications has been associated with improved bladder function in infants with high voiding pressures and low storage volumes.
  - Oxybutynin chloride (Ditropan) inhibit the muscarinic action of acetylcholine on smooth muscle and exerts an antispasmodic effect on bladder smooth muscle (anticholinergic action) leading to its relaxation.
  - Hyoscyamine sulfate (Levbid, Levsin) inhibit the postganglionic cholinergic receptors on smooth muscle cells.
  - Tolterodine (Detrol) is a new more selective antimuscarinic drug targeted for detrusor smooth muscle.
  - Antibiotics
- Patients with history of recurrent UTI may benefit from antibiotic prophylaxis, especially in the presence of vesicoureteral reflux.
  - Prophylactic dosage is usually one quarter of the therapeutic dose administered once per day.
  - More appropriate antibiotics in children include trimethoprim (TMP), sulfamethoxazole (SMZ), nitrofurantoin, and amoxicillin.
  - Trimethoprim and sulfamethoxazole (Bactrim, Septra, Cotrim) alone or in combination with SMZ is the most commonly used antibiotic for both treatment and prophylaxis of UTI.

19.9 Prognosis and Follow-Up

- PUV is a lifelong condition that requires continued medical management.
- Subsequent renal deterioration and bladder changes can be treated and minimized with adequate follow-up care.
- These patients need periodic radiologic and urodynamic evaluation to monitor the upper urinary tract and bladder changes to determine bladder capacity, compliance, and post void residual urine volumes.
- They should have periodic renal sonography and serum creatinine levels.
- Urinary incontinence: Approximately one third of patients with PUVs have problems with diurnal enuresis when older than 5 years. Diurnal enuresis may be caused by the bladder changes that lead to elevated storage pressures and poor emptying.
- Rarely, sphincteric dysfunction secondary to valve ablation can be present. Treatment includes:
  - Anticholinergic medications
  - Clean Intermittent Catheterization (CIC)
  - In some patients, bladder augmentation
- Pulmonary hypoplasia secondary to intrauterine renal dysfunction and oligohydramnios is the primary cause of death.
- Other complications of PUV are generally secondary to chronic bladder changes, leading to elevated detrusor pressures which subsequently lead to progressive renal damage, infection, and incontinence.
- Renal insufficiency and end stage renal disease is expected in those with severe posterior urethral valve.
  - Approximately 25 % of those with PUVs die of renal insufficiency in the first year of life
  - Approximately 25 % of those with PUVs die later in childhood
  - Approximately 50 % survive to adulthood with varying degrees of renal function
  - Today, with good follow-up, early diagnosis and treatment, and advent of better techniques in the treatment of pediatric renal insufficiency, most of these children can be expected to survive. This also include early diagnosis and aggressive treatment of infections and bladder dysfunction.
- There are several risk factors for progression of PUV related complications which include:
  - Elevated nadir creatinine defined as greater than 1 mg/dL measured during the first year of life.

  - Bladder dysfunction with poor compliance
  - Elevated leak point pressures
  - The need for clean intermittent catheterization
- Vesicoureteral reflux:
  - Vesicoureteral reflux is commonly associated with PUVs and is present in as many as one third of patients.
  - Vesicoureteral reflux is generally secondary to elevated intravesical pressures.
  - Therefore, the treatment of vesicoureteral reflux in patients with PUVs involves treatment of intravesical pressures using:
    - Anticholinergics
    - Timed voiding
    - Double voiding
    - Clean intermittent catheterization
    - Bladder augmentation
- Urinary tract infections:
  - Recurrent UTIs are common in patients with PUV.
  - This is predisposed to by several factors:
    - Elevated intravesical pressures predispose these patients to infection, possibly by altering urothelial blood flow.
    - Elevated post void residual urine volumes, leading to stasis of urine.
    - Dilated upper urinary tracts, with or without vesicoureteral reflux.
  - The management and prevention of UTIs include:
    - Lowering bladder pressures by anticholinergic medications
    - Lowering post void residual urine volume via clean intermittent catheterization
    - Administering prophylactic antibiotics
- Urinary incontinence:
  - It is important to follow these patients with urodynamic studies.
  - To improve urinary continence, it is important to:
    - Lower bladder pressure
    - Improve bladder compliance
    - Minimize post void residual urine volume
    - In some, bladder augmentation may be needed
- Over the last 30 years, the prognosis of children with PUV has steadily improved.
- Today, the mortality of patients with PUVs is less than 3 %. This is attributed to several factors including:
  - Early prenatal diagnosis
  - Prompt resolution of bladder obstruction
  - Aggressive treatment of bladder dysfunction
  - Improved surgical techniques
  - Improved dialysis and transplantation techniques
- Approximately one third of patients with PUVs progress to renal insufficiency in their lifetimes.
- An interesting group of patients are those with vesicoureteral reflux dysplasia (VURD) syndrome.
  - In these patients, one kidney is hydronephrotic, nonfunctioning, and has high-grade vesicoureteral reflux.
  - The high-grade reflux is thought to act as a pop-off valve, leading to reduced overall bladder pressures and preservation of contralateral renal function.
  - In the past, these patients were thought to have a better outcome due to preserved renal function in one kidney at the sacrifice of the other.
  - These patients however, may suffer long-term adverse renal function with hypertension, proteinuria, and renal failure.

19.10 Long-Term Outcomes

- The presence of bladder outflow obstruction as a result of PUV will result in an increase in the intravesical pressure.
- This raised intraluminal pressure will be transmitted to the developing kidney leading to:
  - Renal parenchymal apoptosis
  - Abnormal cellular differentiation
  - Glomerular changes
- The extent of these early changes will determine the renal function in later life.
- The degree of obstruction is important in this regard.
- In cases where the obstruction is less severe or declares itself later in pregnancy, the effects of obstruction tend to be more on the bladder and

renal effects are limited to dilatation of the collecting system with minimal disruption of normal nephrogenesis.

- An alternative theory propose that renal dysplasia seen in conjunction with posterior urethral valves is secondary to abnormal position of the ureteric bud and implantation into the metanephric blastema.
- Renal dysfunction seen in patients with posterior urethral valve appears to be the result of varying degrees of inherent dysplasia and the effects of bladder outflow obstruction.
- In post-natal life these changes can be further exaggerated by:
  - Urinary tract infections
  - VUR
  - Bladder dysfunction
- A significant loss of nephrons will lead to hyperfiltration of existing functional nephrons as a result of vasodilatation of the afferent arterioles (glomerular capillary hypertension).
- This compensatory mechanism will decompensates over time.
- The end result is:
  - Glomerulosclerosis
  - Proteinuria
  - Hypertension
  - Reduced glomerular filtration rate
  - Damage to the distal nephron impairs the concentrating ability of the kidney resulting in polyuria and polydipsia (nephrogenic diabetes insipidus)
  - End stage renal failure

19.10.1 Vesico-ureteric Reflux

- At presentation, approximately 50 % of patients with PUV have vesico-ureteric reflux (VUR) on the initial MCUG.
- VUR in these patients is secondary to the bladder outflow obstruction and co-existent bladder dysfunction.
- Approximately 15 % of patients with PUV will have unilateral high grade VUR with ipsilateral non-functioning kidney.
- Following valve ablation the severity of VUR may decrease or resolve completely in 25–50 % of cases, and this improvement is more likely in those presenting as neonates or during infancy.
- Persistent VUR, especially high grade and bilateral, after successful valve ablation is associated with poor long-term renal outcome.
- Anti-reflux procedures in boys with PUV is no longer recommended as this is associated with a high failure rate.
- Patients with high grade VUR and poor function of the ipsilateral kidney are treated with nephrectomy of the non-functioning ipsilateral kidney and bladder augmentation using the dilated ureter.
- A refluxing ureterostomy as a form of urinary diversion can be used also.
- The distal ureter has been used as a Mitrofanoff channel with or without an associated anti-reflux procedure.
- Persistent high grade VUR are treated surgically prior to renal transplant. These are known to be risk factor for recurrent urinary tract infection which has a negative impact on a transplanted kidney.

19.10.2 Hydro-ureteronephrosis

- The majority of neonates presenting with posterior urethral valves will have bilateral hydro-ureteronephrosis.
- Some of these cases will worsen as a result of functional obstruction at the level of uretro-vesical junction which usually resolves within 48–72 h. This is attributed to the thickened trabeculated bladder wall that collapses, pinching off the ureteric orifices following decompression of the urinary bladder. The obstruction is usually followed by post-obstructive diuresis and do not require internal JJ stenting or placement of nephrostomies.
- Other cases of hydro-ureteronephrosis may improve following catheterization.
- Ureteric re-implantation with or without tapering is no longer performed in cases of hydro-ureteronephrosis secondary to PUV.

19.10.3 Bladder Dysfunction

- The importance of bladder dysfunction and its impact outcome on both urinary continence and renal function in boys with posterior urethral valves was recognized.
- This is secondary to in-utero changes in response to outflow obstruction and/or the result of urinary diversion.
- Others believe that urinary diversion does not adversely affect the bladder function but may improve it.
- The 'valve bladder syndrome':
  - This was introduced to encompass several features seen in patients with PUV and include:
    - The abnormal voiding patterns and symptoms of voiding dysfunction
    - The persistent thick walled bladder
    - Incomplete bladder emptying
    - Associated upper urinary tract dilatation
  - Three dominant urodynamic patterns were found in these patients:
    - The hyper-reflexic bladder
    - The hypo-compliant bladder
    - The acontractile bladder
    - Overlap between these patterns may be seen
- Urodynamic abnormalities were observed in 80 % of the overall patient group with PUVs.
- Bladder dysfunction is an important key to long term renal function outcomes.
- Bladder instability and poor compliance correlate with a poor renal functional outcome.
- It was shown that patients with the following features are more likely to progress to end stage renal disease:
  - Severe bladder dysfunction, defined as low compliance with end filling pressure >40 cm of H_2O
  - Post-void residual volume >30 %
  - Underactive detrusor
  - Patients in need for clean intermittent catheterization (CIC)

19.10.4 Renal Transplantation

- A significant number of boys with PUV progress to end-stage renal failure.
- These patients will need renal transplantation.
- Urinary bladder assessment is an important part of the pre-transplant work-up of these patients.
- A high pressure, poorly compliant, low bladder capacity may risk the transplanted kidney with the possibility of graft loss.
- These patients are managed with bladder augmentation which can be performed prior to or after renal transplantation.
  - Bladder augmentation cystoplasty with/without a catheterisable conduit performed prior to renal transplant allows postoperative healing without immunosuppression but risks a 'dry cystoplasty' which must be managed by bladder cycling and lavages.
  - Bladder augmentation cystoplasty can be performed after renal transplantation and in these, it is important that immunosuppression requirements have been stabilized and the improved renal function offers clear advantages. The transplanted ureter may be reimplanted into the native bladder or brought out as a cutaneous ureterostomy.
  - The 5 year renal graft survival rates in the PUV have improved over the last two decades from 40 % in the 1980s to near 70 % in the 1990s.

19.10.5 Fertility

- The following factors influence the efficacy of ejaculation in patients with posterior urethral valves:
  - Persisting dilatation of the posterior urethra
  - Damage to tissues around the verumontanum
  - Secondary urethral strictures resulting from previous surgery
- Erectile dysfunction is seen more commonly in patients with chronic kidney disease and those on dialysis.
- The majority of these patients however, will have a semen analysis that is considered within the normal range.

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Utricular Cyst (Prostatic Utricular Cyst)

20

20.1 Introduction

- The prostatic utricle is a small, epithelium-lined diverticulum of the prostatic urethra.
- Utricle is derived from the Latin word "pouch," which forms a cul-de-sac. The prostatic utricle (pouch of the prostate) is a small diverticulum (6 mm long) in the prostatic urethra (Fig. 20.1).
- It is located in the verumontanum (seminal colliculus) between the two openings of the ejaculatory ducts and extends backward and slightly upward for a very short distance within the medial lobe of the prostate.
- It is also known as the vagina masculina or vesicula prostatica.
- It is a normal anatomic variant representing the remnant of the fused caudal ends of the Müllerian ducts. This origin is occasionally disputed.
- It is considered to represent the male homologue of the female uterus and vagina.
- In 1905, Robert William Taylor stated the function of the prostatic utricle thusly: "In coitus it so contracts that it draws upon the openings of the ejaculatory ducts, and thus renders them so patulous that the semen readily passes through."
- Utricle cysts always arise from the level of the verumontanum and are always in the midline.
- The cyst typically lies between the bladder and the rectum and, thus, is palpable on per rectal exam in 50 % of the cases.
- They are variable in size but are usually small in size (commonly <10 mm). They can however grow to reach a large size.
- Morphologically, prostatic utricle cyst appears as a small, single, smooth, unilocular cyst of variable size.
- The cyst lining can be:
  - Cuboidal
  - Columnar
  - Squamous or transitional type

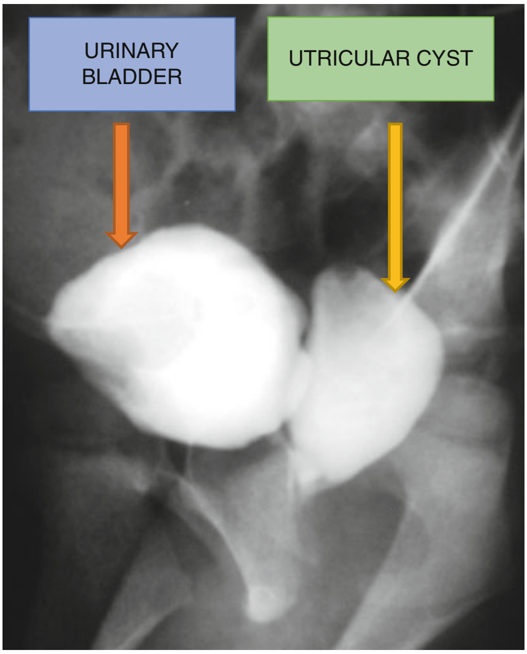

Fig. 20.1 A micturating cystogram showing a large utricular cyst

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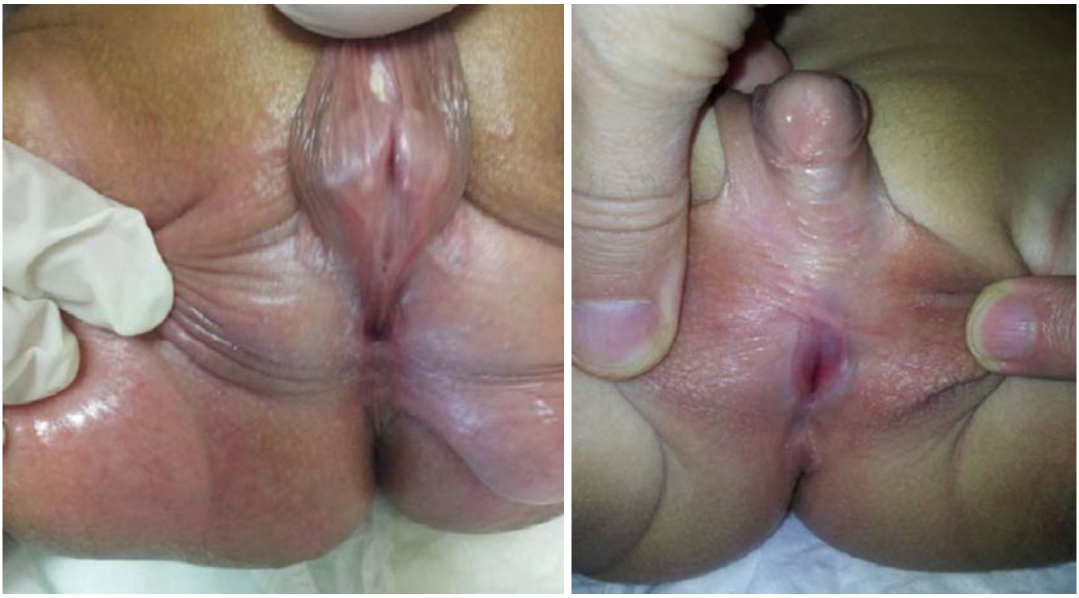
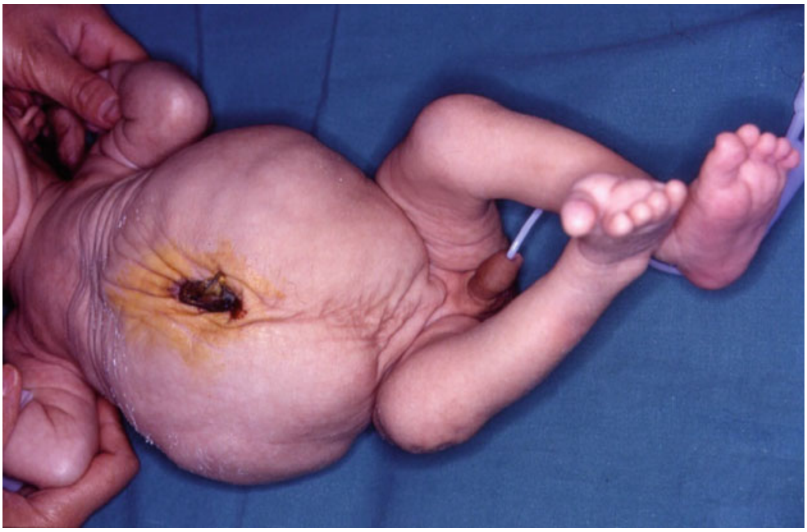
A.H. Al-Salem, *An Illustrated Guide to Pediatric Urology*, DOI 10.1007/978-3-319-44182-5_20



Figs. 20.2 and 20.3 Clinical photographs showing severe hypospadias. This is known to be associated with utricular cyst. The increasing severity of the hypospadias correlates with increasing size of the utricle

Fig. 20.4 A clinical photograph showing Prune belly syndrome which is known to be associated with utricular cyst



- Prostatic utricle cyst is usually seen during the first to second decades of life, with a mean age range of 26 years.
- There is an association between utricular cysts and:
  - Renal agenesis/dysgenesis (10–25 %)
  - Hypospadias (25 %) (Figs. 20.2 and 20.3)
  - Prune-belly syndrome (Fig. 20.4)
  - Anorectal agenesis
  - Down's syndrome
- Hypospadias is considered the most commonly associated malformation with the prostatic utricle (14–47 %), and the increasing severity of the hypospadias correlates with increasing size of the utricle (Figs. 20.2 and 20.3).

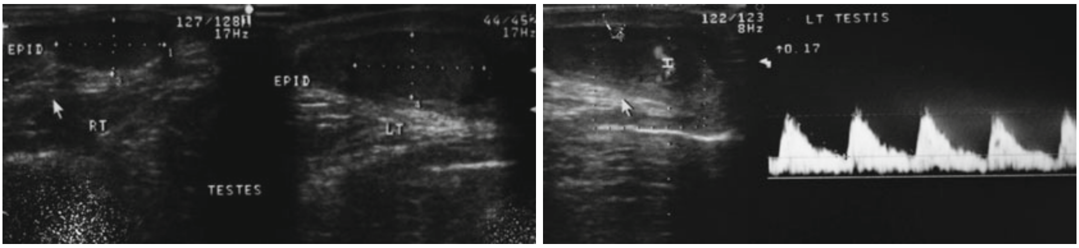
- Normally, the prostatic utricle distends with urine during voiding and then passively drains.
- Poor emptying leads to urine retention and stasis and this leads to complications including:
  - Recurrent urinary tract infection
  - Hematuria
  - Urethral discharge
  - Recurrent epididymitis
  - Voiding dysfunction
  - Urine retention
  - Post voiding urine drippling
  - Stone formation within the utricle cyst
  - Malignant transformation (e.g. clear cell carcinoma, or squamous cell carcinoma) with a reported prevalence as high as 3 %.
- Utricular cyst is rare but along with its rarity, it presents a challenge in its diagnosis and proper management. Awareness of this is important.
- Persistence or untreated prostatic cyst could be a cause of infertility.
- The differential diagnoses include mullerian duct cysts, bladder diverticulum, cystic teratoma, seminal vesicle cyst, epididymal cyst and Wolffian duct cyst.

20.2 Embryology

- Embryologically, in the male fetus the Mullerian ducts regress under the influence of anti-Mullerian hormone (Mullerian inhibiting substance).
- This is a glycoprotein secreted by the Sertoli cells of the fetal testes at eight gestational weeks.
- Persistence of the Mullerian ducts as result of failure of synthesis or action of Mullerian inhibitory substance results in persistent Mullerian duct syndrome.
- This is characterized by the presence of uterine tissue and fallopian tubes in a phenotypic and genotypic male.
- Utricular cysts are thought to result from incomplete regression of the Mullerian ducts or incomplete androgen-mediated closure of the urogenital sinus caused by an error in the production or sensitivity to local testosterone or anti-Mullerian hormone.
- These cysts are differentiated anatomically from Mullerian duct cysts.
  - Utricular cysts:
    - Always in the midline
    - They present during the first to second decade of life
    - They communicate with the urethra
    - They have a tubular or vesicular shape
    - The majority are seen in younger patients
    - They have an association with unilateral/bilateral renal agenesis, and hypospadias
    - They can be visualized with a micturating cystourethrogram or a retrograde urethrogram.
  - Mullerian duct cysts:
    - Usually seen above the prostate
    - They are seen in the older age group ranging from 2 to 75 years
    - Mullerian duct cysts generally do not communicate with the urethra
    - They cannot be visualized with a micturating cystourethrogram or a retrograde urethrogram.
    - It is proposed that these cysts originate due to failure of fusion of Mullerian duct resulting from deficient Mullerian inhibitory factor.
    - They are associated with intersex conditions
    - They are also seen in those with normal external genitalia
    - Based on this, it has been postulated that the Mullerian duct cysts are the remnants of the paramesonephric ducts rather than the Mullerian ducts.

20.3 Classification of Utricular Cysts

- Ikoma et al. in 1985 classified utricular cysts into four types depending on the size of the cyst and the site of communication with the urethra.



Figs. 20.5 and 20.6 Testicular ultrasound and Doppler ultrasound of a child with acute scrotum. Note the enlarged left epididymis which was found to be secondary to a utricular cyst

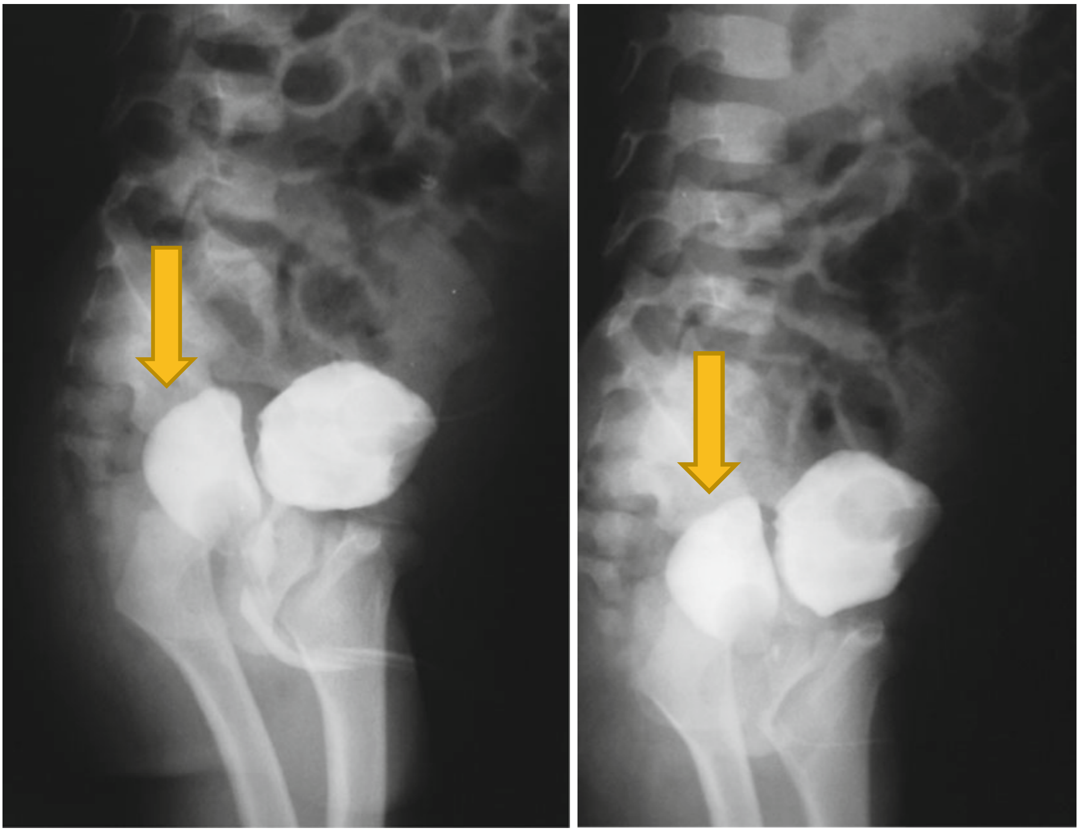
- This classification was based on urethrographic configuration.
  - Grade 0: The utricle opening is located on the posterior urethra but the utricle does not extend over the verumontanum.
  - Grade I: The utricular cyst is larger than grade 0 but the cyst does not reach the bladder neck.
  - Grade II: The utricular cyst is more enlarged and its dome extends over the bladder neck.
  - Grade III: In grades 0, I, and II, the prostatic utricle opens into the central area of the verumontanum, but when the opening is situated in the bulbous urethra just distal to the external sphincter, this is classified as grade III.

20.4 Clinical Features

- Utricular cyst is a very rare congenital anomaly that arises from incomplete regression of the Mullerian ducts and commonly seen in males with perineal or penoscrotal hypospadias and in intersex disorders.
- Usually they are asymptomatic discovered incidentally.
- The presentation of utricular cysts is variable, and because many are asymptomatic, they escape detection.
- A prostatic utricle cyst is usually small in size and asymptomatic.
- A small prostatic utricle is occasionally seen as an incidental finding on routine VCUG as a tiny diverticulum of a few millimeters in length or on rare occasions measuring up to 1 cm.
- A large prostatic utricle is more often associated with male hypospadias. This is more commonly seen in those with proximal penile, penoscrotal and perineal hypospadias.
- This must be kept in mind as patients with a large prostatic utricle, direct catheterization of the bladder during surgical repair of hypospadias or during VCUG may be difficult secondary to preferential passage of the catheter into the utricle.
- The clinical presentation of utricular cyst is variable and include (Figs. 20.5 and 20.6):
  - Recurrent UTI
  - Recurrent epididymitis
  - Hematuria
  - Pyuria
  - Urinary incontinence
  - Urine retention
  - Post void urinary drippling
  - Constipation
  - A pelvic mass
  - Suprapubic or rectal pain
- Rarely it may enlarge and present as an abnormal lower abdominal or pelvic mass.
- When enlarged, it may be observed during pelvic or CT-scan as a fluid filled cavity between bladder and rectum.

20.5 Investigations

- These patients should be investigated including abdominal and pelvic ultrasound and CT scan as well as a micturating cystourethrogam and or an ascending urethrogram.
- Voiding cystourethrogram (VCUG) and retrograde urethrography (RUG) can define the



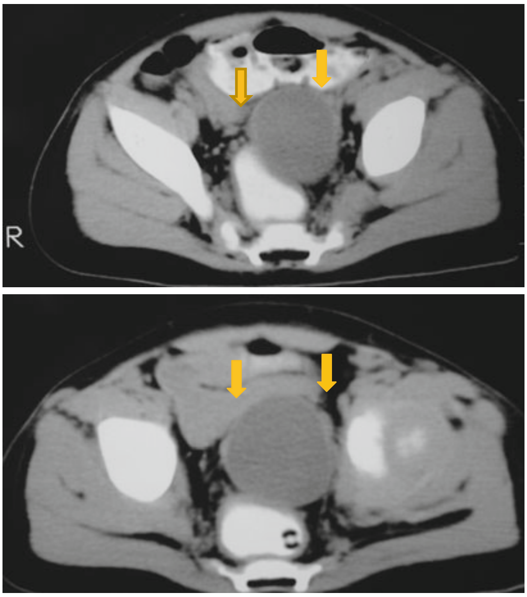
Figs. 20.7 and 20.8 A micturating cystourethrogram showing a large utricular cyst which is arising from the prostatic urethra. Note the large size of the cyst and its location

utricle size, which usually ranges from a few millimeters to more than 2 cm.

- VCUG is important to define the site of the cyst and its relation to the urethra as well as its size (Figs. 20.7 and 20.8).
- CT-scan will localize the site of the cyst, its shape and size as well as its relation to the urinary bladder and rectum (Figs. 20.9, 20.10, and 20.11).
- MRI can easily identify these cysts by virtue of their high signal on T2-weighted images but this investigation is reserved for cases that are difficult to diagnose by the more common and simpler investigations.

20.6 Treatment

- Surgical excision is the treatment of choice for symptomatic utricular cysts.



Figs. 20.9 and 20.10 CT-scans showing a large utricular cyst

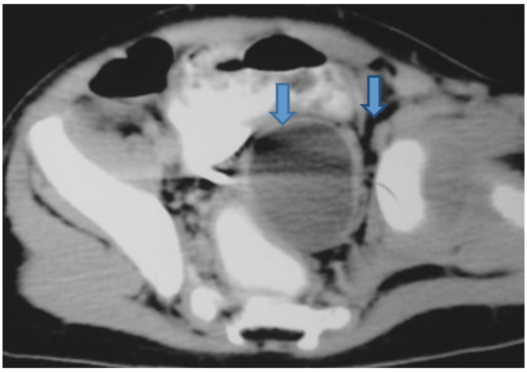
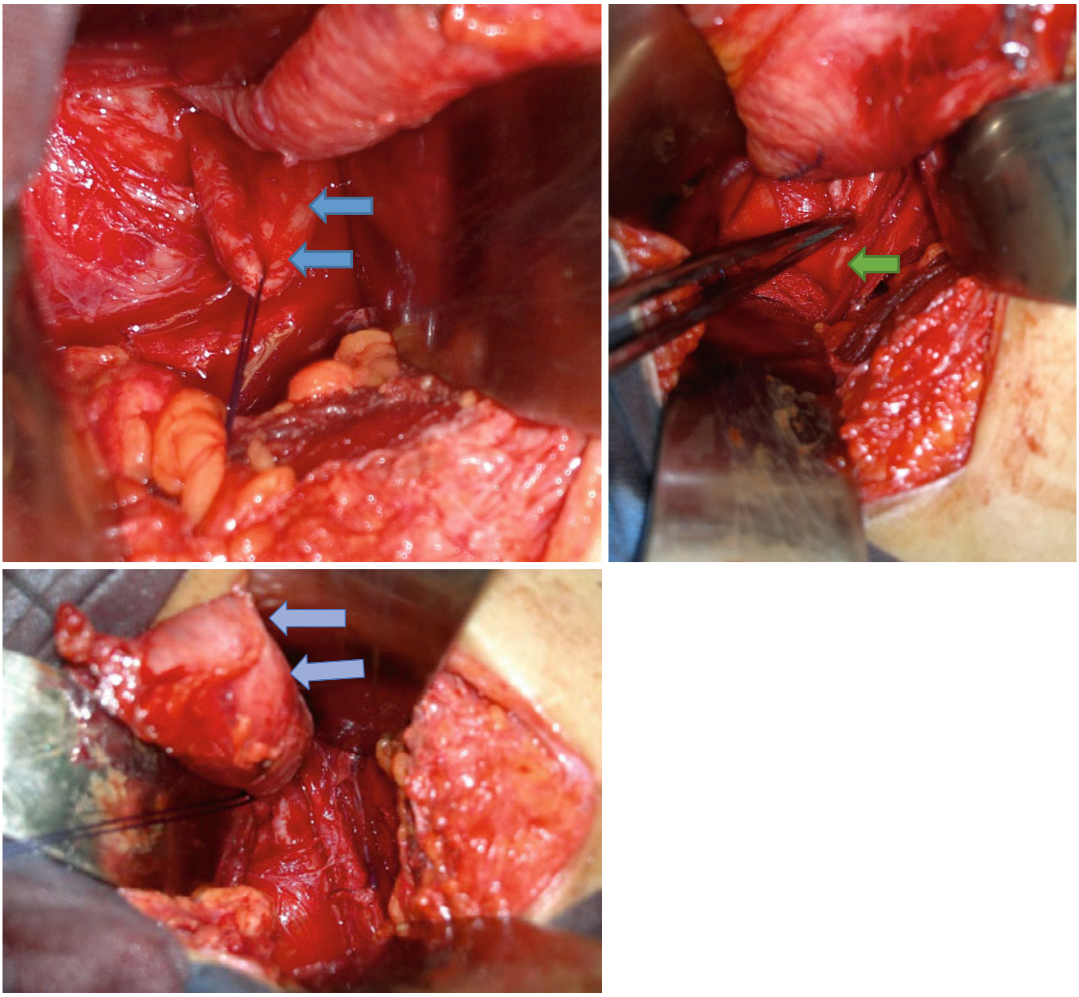


Fig. 20.11 CT-scan showing a large utricular cyst

- Surgical management of prostatic utricle cyst remains challenging, because of the rarity of this disorder and due to the close proximity of these lesions to the ejaculatory ducts, pelvic nerves, rectum, vas deferens and ureters.
- Surgical treatment should be reserved for symptomatic utricle cysts only.
- The definitive treatment of symptomatic utricular cyst is surgical excision but the approach remains controversial.
- Several surgical approaches have been described including:
  - Endoscopic transurethral cyst catheterization and aspiration
  - Cyst orifice dilatation
  - Incision and deroofing
  - Transperineal cyst aspiration and sclerotherapy
  - Electrofulgaration
  - Open excision (perineal, suprapubic extravesical, transperitoneal, parasacral, transvesical, transtrigonal, retropubic, posterior and anterior sagittal with rectal retraction, and transrectal posterior or anterior sagittal approach)
  - Laparoscopic excision
  - Robot-Assisted Laparoscopic Excision of Prostatic Utricle Cyst
- A suprapubic extravesical and extraperitoneal approach is a relatively easy and direct approach. Such an approach was however reported to have a high rate of incomplete excision. It is feared that total excision may compromise fertility by traumatically damaging or accidentally excising both vas deference because of their close proximity or more commonly insertion in the utricular cyst. The importance of this need to be emphasizes and a preoperative thorough discussion with the parents in this regard is of paramount importance (Figs. 20.12, 20.13, and 20.14).
- Surgical complications include:
  - Incomplete excision
  - Impotence
  - Excision of one or both seminal vesicles
  - Excision of one or both vas
  - Excision of portions of the prostate
  - Rectal injury

20.7 The Müllerian Duct Cyst

- The müllerian duct cyst is a remnant of the caudal ends of the fused müllerian duct, a structure that typically regresses in utero.
- These cysts are typically located in the midline, posterior to the bladder and above the prostate.
- Mullerian duct cysts generally do not communicate with the urethra
- Müllerian duct cysts do not communicate with the prostatic urethra, but are connected to the verumontanum by a thin stalk.
- Unlike utricular cysts, the müllerian duct cyst is not typically associated with other congenital abnormalities of the urinary tract and usually occurs as an isolated entity.
- Rarely, a müllerian duct cyst may be associated with renal agenesis.
- Rarely, calculi may occur within these cysts.
- The peak clinical incidence of müllerian duct cysts occurs in the age range of 20–40 years, as the cyst becomes larger and accumulates fluid.
- The clinical presentation is varied, including:
  - Urinary frequency
  - Urinary urgency
  - Dysuria
  - Urinary obstruction
  - Hematuria
  - Pelvic pain
- Digital rectal examination may reveal a midline cystic mass superior to the prostate gland.



Figs. 20.12, 20.13, and 20.14 A clinical intraoperative photograph showing a large utricular cyst being excised. Note its large size and its relation to the vas deference

- A müllerian duct cyst can be noted on a voiding cystourethrogram or an intravenous urogram, manifesting as an impression along the posterior wall of the bladder. A müllerian duct cyst does not communicate with the urethra and so will not be seen on a voiding cystourethrogram.
- Pelvic ultrasound and transrectal ultrasound will reveal a fluid-filled cyst projecting posterior and superiorly from the prostate, extending posterior to the urinary bladder.
- MRI is a valuable imaging modality for the evaluation of müllerian duct cysts.
- The müllerian duct cyst and utricle cyst both occur in the midline; however, the utricle cyst is typically smaller, confined to the base of the prostate, and communicates with the posterior urethra.
- Müllerian duct cysts are larger and extend above the base of the prostate.

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Hypospadias

21

21.1 Introduction

- The term hypospadias is derived from the Greek words hypo (below, too little) and Spadone (crack, gutter).
- Hypospadias is defined as the combination of three anatomical abnormalities of the penis (Figs. 21.1, 21.2, 21.3, and 21.4):
  - Ectopic proximally placed meatus which may be located on the ventral side of the penis at any position between the tip of the glans and the perineum.
  - A dorsal winged prepuce and lack of ventral prepuce.
  - A ventral penile shaft deviation.
  - The second and third characteristics may not necessarily be present.
  - The megalomeatus is an exception as it is characterized by a complete prepuce and a coronal lying meatus adjacent to a non-closed-glans with an open navicular fossa. This is also called (MIP) Megameatus with Intact Prepuce (MIP) variant of hypospadias.
- Hypospadias is caused by the arrest of normal development of the urethra, at various stages of embryonic development (9–13 weeks of pregnancy).
- Hypospadias is among the most common birth defects in males.
- The exact incidence of hypospadias is not known but it has been estimated that hypospadias affects approximately 1 of every 200–250 male live newborns.
- The incidence of hypospadias is higher in whites than in blacks.
- Hypospadias is more common in Jewish and Italian people.
- Hypospadias is also more common in the Caucasian population followed by African-Americans and then the Hispanic Americans.
- The incidence of hypospadias is reported to be increasing in both Europe and North America from an incidence of 20.2 per 10,000 in 1970 to a current incidence of 39.7 per 10,000 children born in the U.S.A.
- The reason for this increase is not exactly known
- There is a definite familial occurrence of hypospadias. This is estimated to be about 7 %.
- In approximately 80–90 % of cases, hypospadias is of the distal part while the remaining 10–20 % have proximal hypospadias.
- There is an increased probability for the occurrence of hypospadias in the following situations:
  - Father with hypospadias
  - Low birth weight
  - Twin or triplet births
  - Maternal iron supplements
  - Smoking mothers
  - Fathers with pesticide contact
- Chordee is fibrous remnant of the corpus spongiosum distal to the meatus. It extends in a V shape on both sides, and acts by the lack

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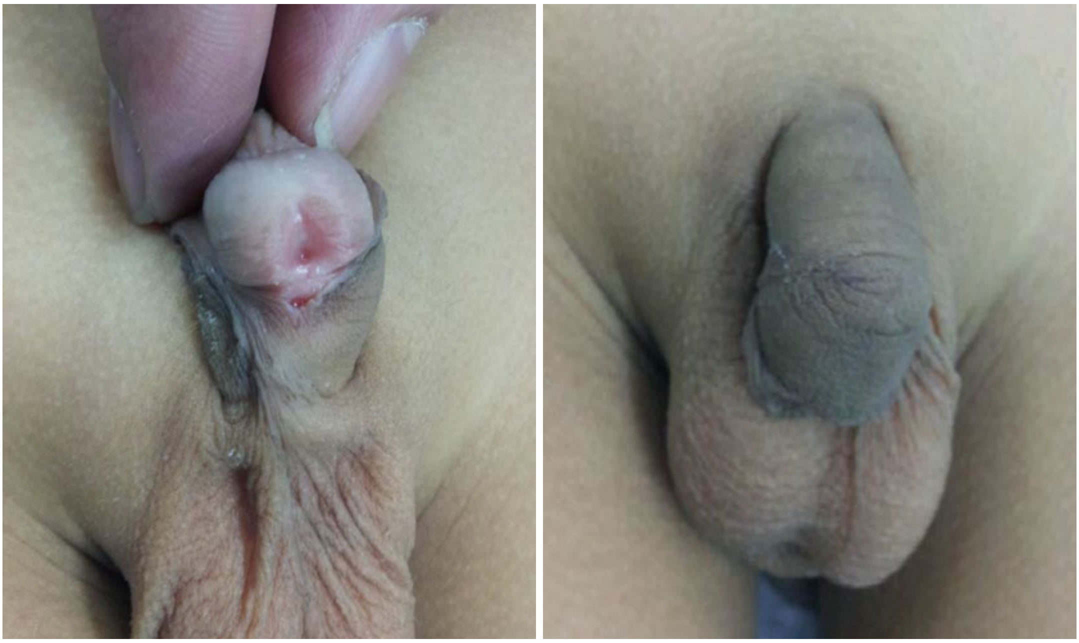
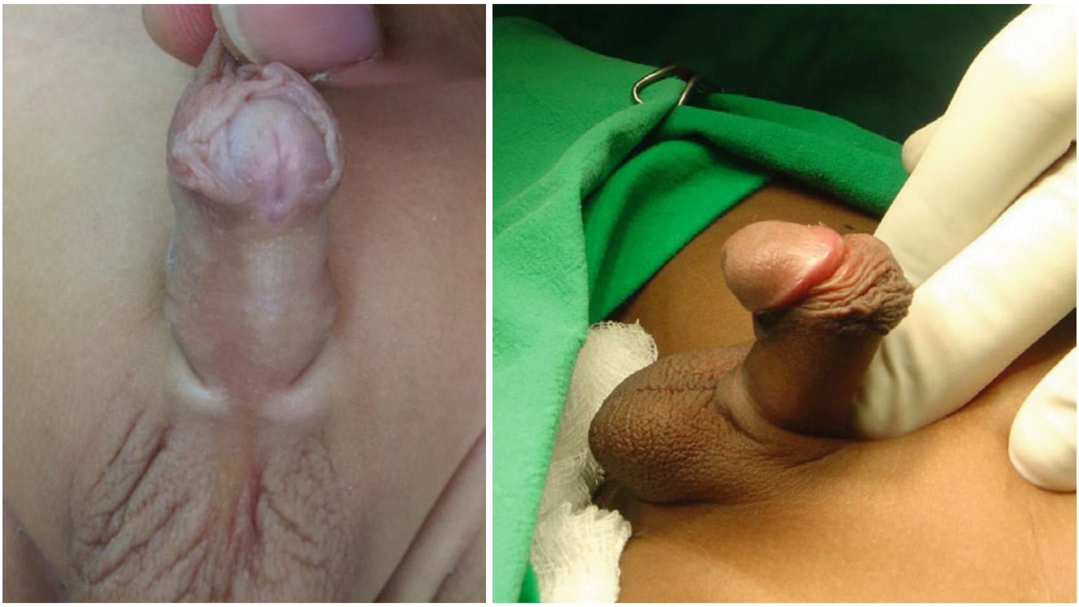


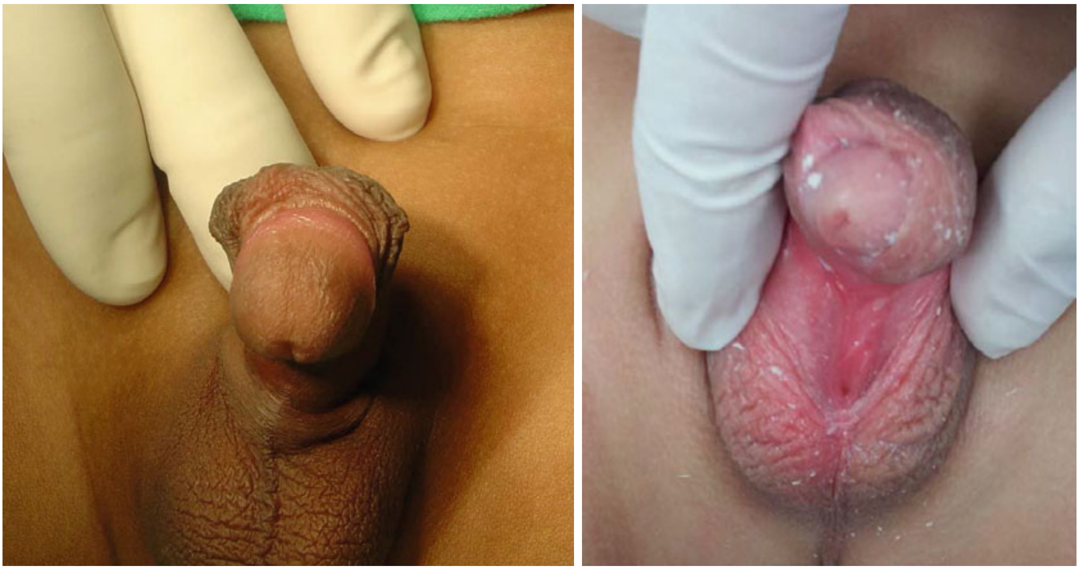
Figs. 21.1 and 21.2 Clinical photographs showing two patients with hypospadias. The ectopic urethra is located on the ventral side of the shaft penis. Note the ectopic urethral meatus and also the dorsal winged prepuce

of elasticity producing a ventral deformity (Figs. 21.5 and 21.6).

- Chordee (downward bending of the penis) is another feature of hypospadias seen more commonly in those with proximal hypospadias. This is found in 10 % of distal hypospadias and 50 % of proximal hypospadias.

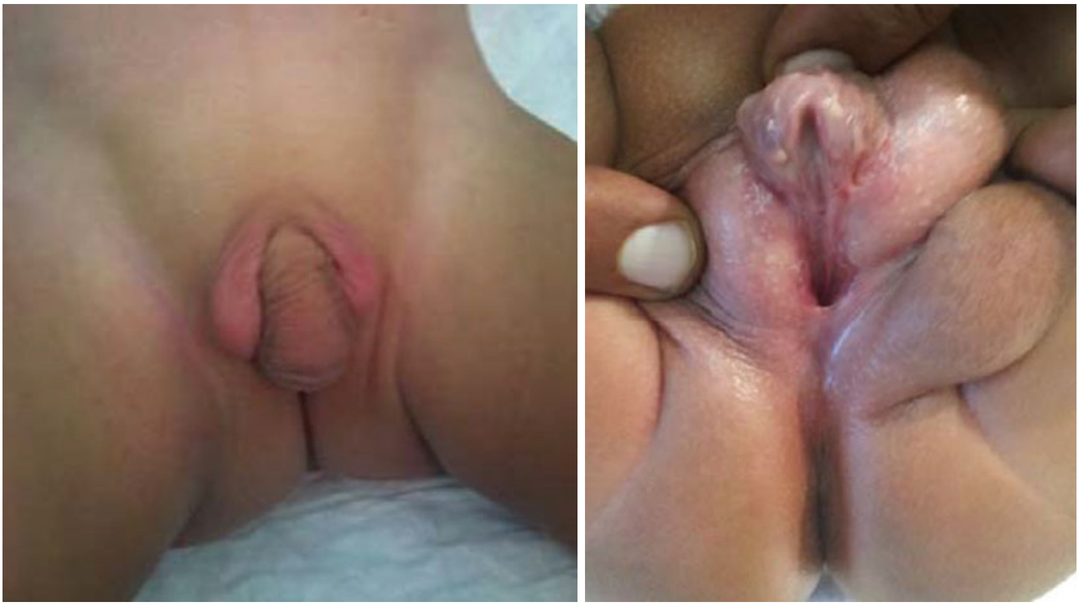


Figs. 21.3 and 21.4 Clinical photographs showing two patients with hypospadias. Note the lack of prepuce ventrally. Note also the ventral curvature of the penis



Figs. 21.5 and 21.6 Clinical photographs of two patients with hypospadias. Note the shape of chordee and the ventral curvature of the penis

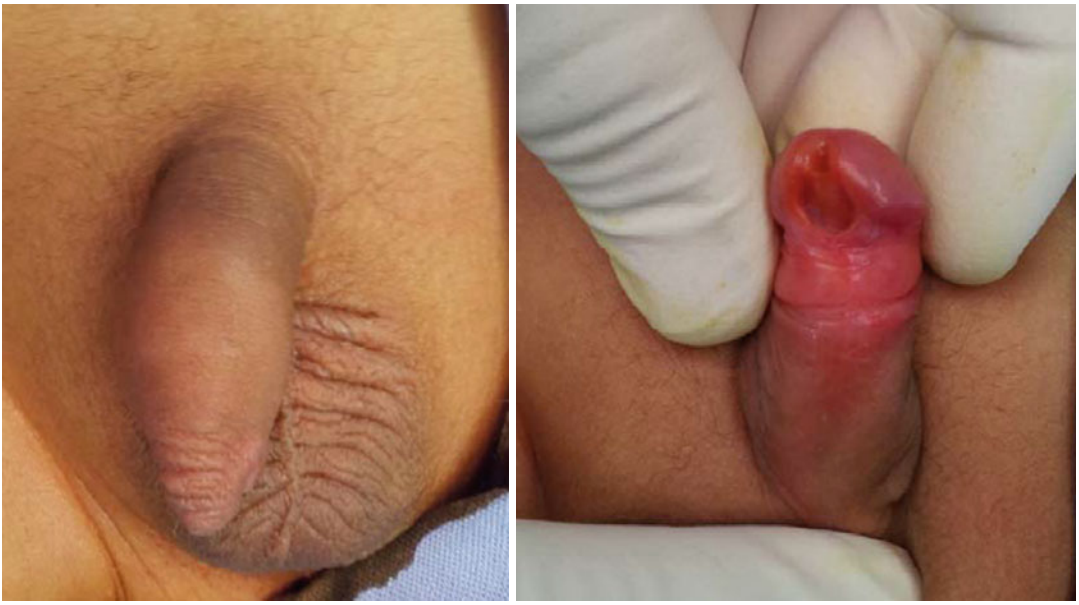
- Scrotal transposition is seen usually in patients with more proximal hypospadias and it is associated with bifid scrotum (Penoscrotal transposition and bifid scrotum) (Figs. 21.7 and 21.8).
- Characteristically, in the majority of patients with hypospadias the foreskin is underdeveloped and does not wrap completely around the penis, leaving the underside of the glans penis



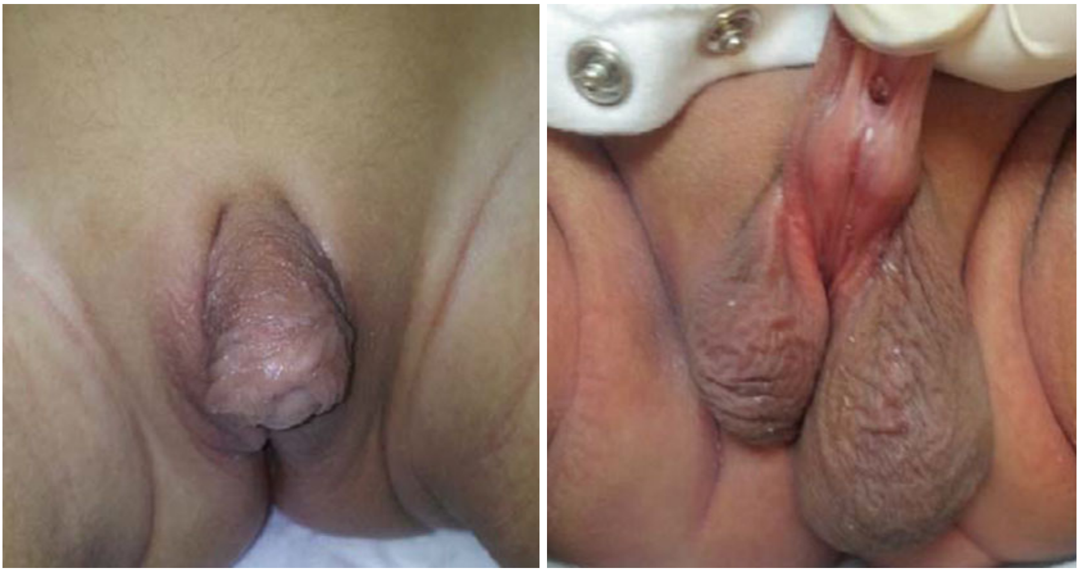
Figs. 21.7 and 21.8 Clinical photographs showing scrotal transposition in two patients with hypospadias. Note the severe hypospadias in the second photograph

uncovered by foreskin (Hooded foreskin). The only exception to this is the megameatus.

- It must be emphasized that not all newborns with partial foreskin development have hypospadias, as some have a normal urinary opening with a hooded foreskin (This is called "chordee without hypospadias").
- Megameatus with intact prepuce (MIP) variant of hypospadias occurs when the foreskin is normal and there is a concealed hypospadias. The condition is discovered during newborn circumcision or later in childhood when the foreskin begins to retract (Figs. 21.9 and 21.10).
- The most common associated defect with hypospadias is an undescended testicle, which has been reported in approximately 3 % of infants with distal hypospadias and 10 % of those having proximal hypospadias (Figs. 21.11 and 21.12).
- In patients with proximal hypospadias, a karyotype and endocrine evaluation should be performed to detect disorders of sexual development or hormone deficiencies.
- Using modern surgical techniques, a normal appearing penis can usually be expected from hypospadias repair.
- Hypospadias repair should be performed only by experienced surgeons and at centers with extensive experience.
- To emphasize this, Duckett in 1995 coined the concept of hypospadiologists (surgeons who subspecialize in hypospadias repair).
- Currently, hypospadias is repaired not only for functional reasons but also for cosmetic reasons.
- The postoperative penis should:
  - Be suitable for normal voiding
  - Be suitable for future sexual intercourse
  - Have an acceptable cosmetic appearance
- More than 300 different types of repairs have been described in the medical literature.
- The most common operation to repair hypospadias is the tubularized incised plate or "TIP" repair. This procedure can be used for all distal hypospadias repairs.
- There are several techniques to repair proximal hypospadias as a single stage or two stage operations.
- There are several factors that contributed recently to increased success of hypospadias repair. These include:



Figs. 21.9 and 21.10 Clinical pictures of one patient with megameatus. Note the complete normal looking foreskin. Note the size of the meatus after retracting the foreskin



Figs. 21.11 and 21.12 Clinical photographs of two patients with hypospadias and undescended testes. In the first one, there are bilateral undescended testes while in the second one there is unilateral undescended testis

  - Better understanding of the anatomy of the penis
  - Improved anesthetic techniques
  - Fine instrumentations and sutures
  - Improved dressing materials, and antibiotics

21.2 Effects of Hypospadias

- Abnormal urinary stream. The more proximally ectopic the position of the urethral meatus, the more likely the urinary stream is to be deflected downward. Any element of chordee can exacerbate this abnormality.
- Fertility may be affected as hypospadias may preclude effective insemination.
- Painful erection
- Psychological stress

21.3 Embryology

- Hypospadias is a congenital defect that is thought to occur during urethral development.
- This occurs between 8 and 20 weeks' gestation.
- Embyologically, the external genitalia are identical in males and females until about 8 weeks' gestation.
  - In males, the external genitalia develop a masculine phenotype under the influence of testosterone.
  - Testesterone is converted to dihydrotestesterone under the influence of 5-alpha reductase.
  - Dihydrotestesterone acts locally to change the external genitalia into a masculine phenotype.
  - As the phallus grows, the open urethral groove extends from its base to the level of the corona.
  - The urethral folds coalesce in the midline from base to tip, forming a tubularized penile urethra and median scrotal raphe.
  - This accounts for the posterior and middle parts of the urethra.
  - The anterior or glanular urethra is thought to develop in a proximal direction, with an ectodermal core forming at the tip of the glans penis, which canalizes to join with the more proximal urethra at the level of the corona.
  - The higher incidence of subcoronal hypospadias supports the vulnerable final step in this embryological theory of development.

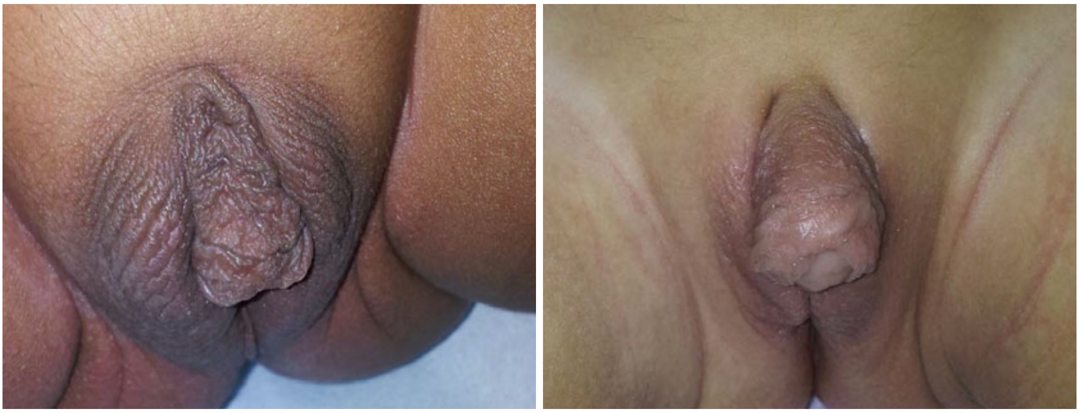
- In 2000, Baskin proposed a modification of this theory in which the urethral folds fuse to form a seam of epithelium, which is then transformed into mesenchyme and subsequently canalizes by apoptosis or programmed cell resorption. Similarly, this seam theoretically also develops at the glanular level, and the endoderm differentiates to ectoderm with subsequent canalization by apoptosis.
- The prepuce normally forms as a ridge of skin from the corona that grows circumferentially, fusing with the glans. Failure of fusion of the urethral folds in hypospadias impedes this process, and a dorsal hooded prepuce results.
- On rare occasions, a glanular cleft with intact prepuce may occur. This is termed the megameatus intact prepuce (MIP) variant.
- Chordee (ventral curvature of the penis) is often associated with hypospadias, especially the more proximal forms of hypospadias.
  - This is thought to result from a growth disparity between the normal dorsal tissue of the corporal bodies and the attenuated ventral urethra and associated tissues.
  - Rarely, the abortive spongiosal tissue and fascia distal to the urethral meatus forms a tethering fibrous band that contributes to the chordee.

21.4 Etiology of Hypospadias

- The etiology of hypospadias is multifactorial but in the majority (65–75 %) the cause remains unknown.
- There has been several etiological factors for hypospadias.
- Several etiologies for hypospadias have been suggested, including genetic, endocrine, and environmental factors.
  - Defects in the androgen synthesis or its action during embryogenesis (A defect in testosterone biosynthesis).
  - Mutations in the 5-alpha reductase enzyme, which converts testosterone to the more potent dihydrotestosterone (DHT).
  - There is a fivefold increased risk of hypospadias in males born through IVF. This may be related to maternal exposure to progesterone, which is commonly administered in IVF protocols. Progesterone is a substrate for 5-alpha reductase and acts as a competitive inhibitor during the process of conversion of testosterone to DHT.
  - Hypospadias is also found in the most common disorder of sex development, the familial male pseudohermaphroditism.
  - Ingestion of substances with estrogenic activity, such as insecticides, natural estrogens, organic products from the manufacture of plastics and pesticides, which are included in food.
  - A higher incidence of hypospadias in winter conceptions has also been proposed.
  - Increased estradiol concentration in placental basal syncytiotrophoblasts of boys with undescended testes.
  - A genetic predisposition to hypospadias.
    - There is a genetic predisposition to hypospadias.
    - The inheritance is likely polygenic.
    - There is an eight times increased in incidence of hypospadias among monozygotic twins.
    - Hypospadias was also shown to be familial.
    - The probability to have a second child with hypospadias is 14 % if the first child has hypospadias.
    - If the father has hypospadias, the probability that one of his sons suffers from the same pathology is 8 %.
- Hypospadias is present in many syndromes, such as Smith-Lemli-Opitz syndrome or Robinow syndrome.
- Hypospadias is associated with increasing parity, increasing maternal age, and low birth weight.

21.5 Associated Anomalies

- A patent processus vaginalis (9 %)
- Undescended testes and inguinal hernias are the most common anomalies associated with hypospadias.



Figs. 21.13 and 21.14 Clinical photographs showing severe hypospadias and bilateral undescended testes

- The incidence of undescended testes and inguinal hernias with hypospadias is about 9 % for each.
- Undescended testis is seen in about 5 % of mild forms of hypospadias (Figs. 21.13 and 21.14).
- The incidence of undescended testes is more than 30 % in those with more proximal hypospadias.
- The incidence of inguinal hernias is about 20 % in those with more proximal hypospadias.
- The combination of hypospadias and undescended testis should raise the possibility of an underlying disorder of sexual development (DSD) (Fig. 21.15).
- DSD were identified in approximately 30 % of patients with unilateral or bilateral undescended testes and hypospadias. The incidence approaches 50 % in those with nonpalpable testes but if the testes are palpable, the incidence is only 15 %.
- The more proximal hypospadias have a higher association with DSD.
- A prostatic utricle is another association with hypospadias. This is more likely so in those with more proximal hypospadias.
- Sometimes hypospadias is associated with a low-grade vesicoureteral reflux (Fig. 21.16).
- Upper urinary tract anomalies are rarely associated with hypospadias and do not justify routine imaging in these patients.

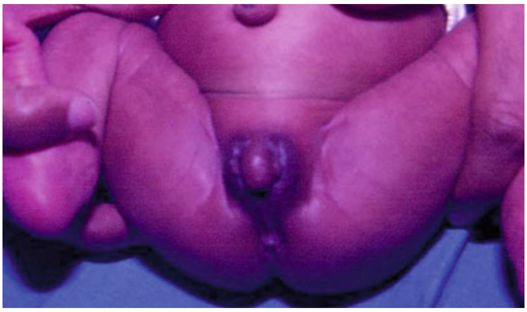


Fig. 21.15 A clinical photograph showing a newborn with disorder of sexual development resembling hypospadias clinically

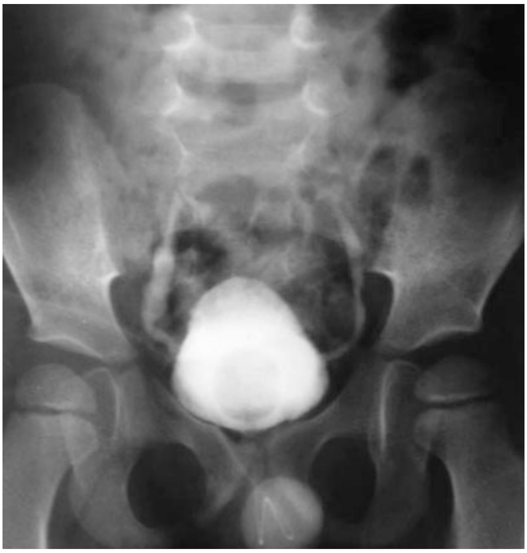
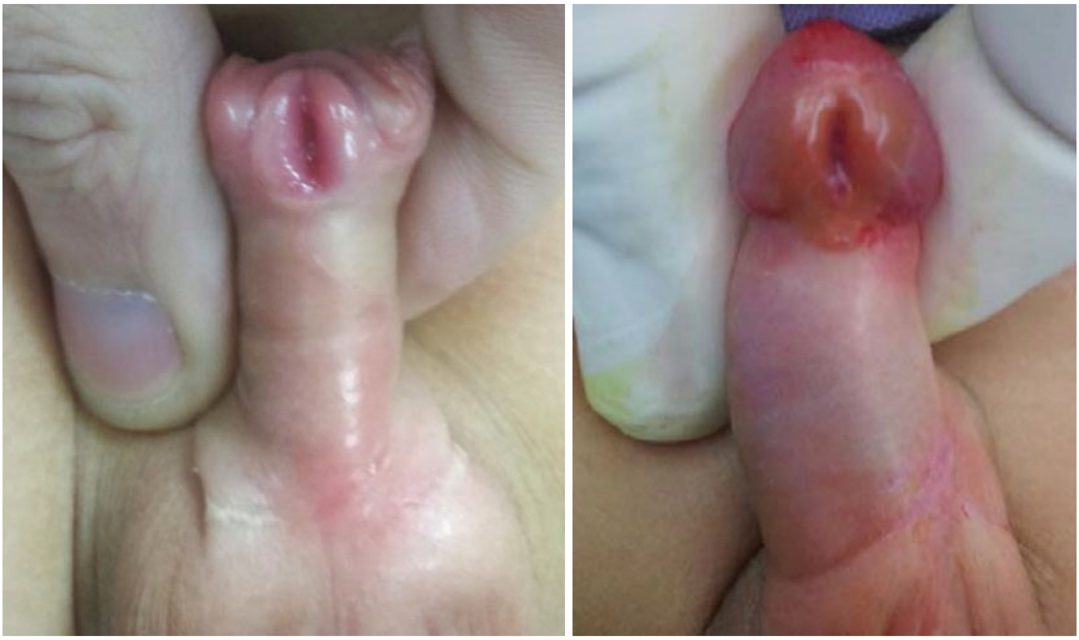


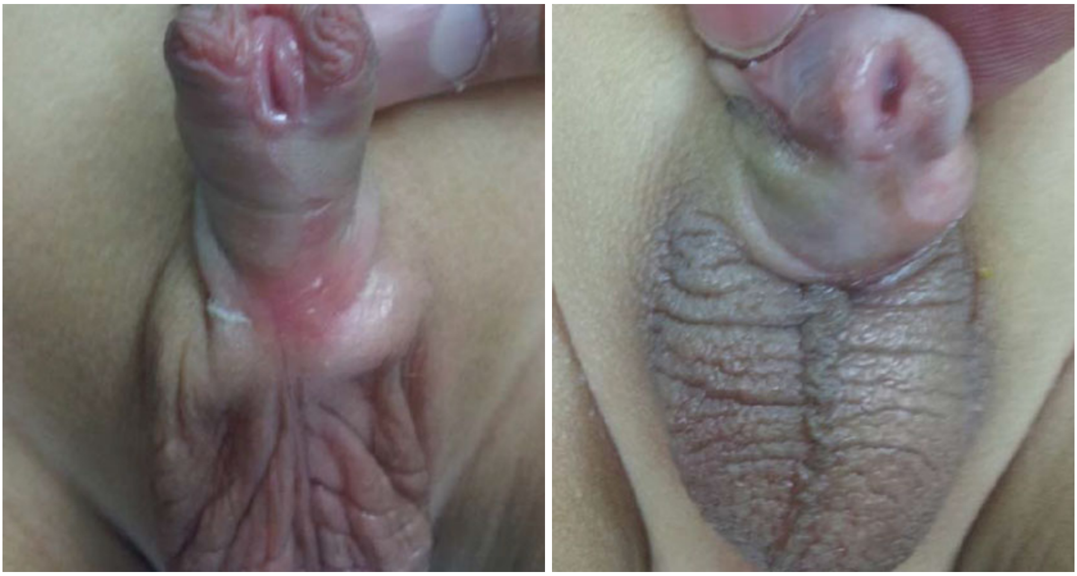
Fig. 21.16 A micturating cystourethrogram showing mild vesicoureteral reflux in a patient with hypospadias

21.6 Classification of Hypospadias

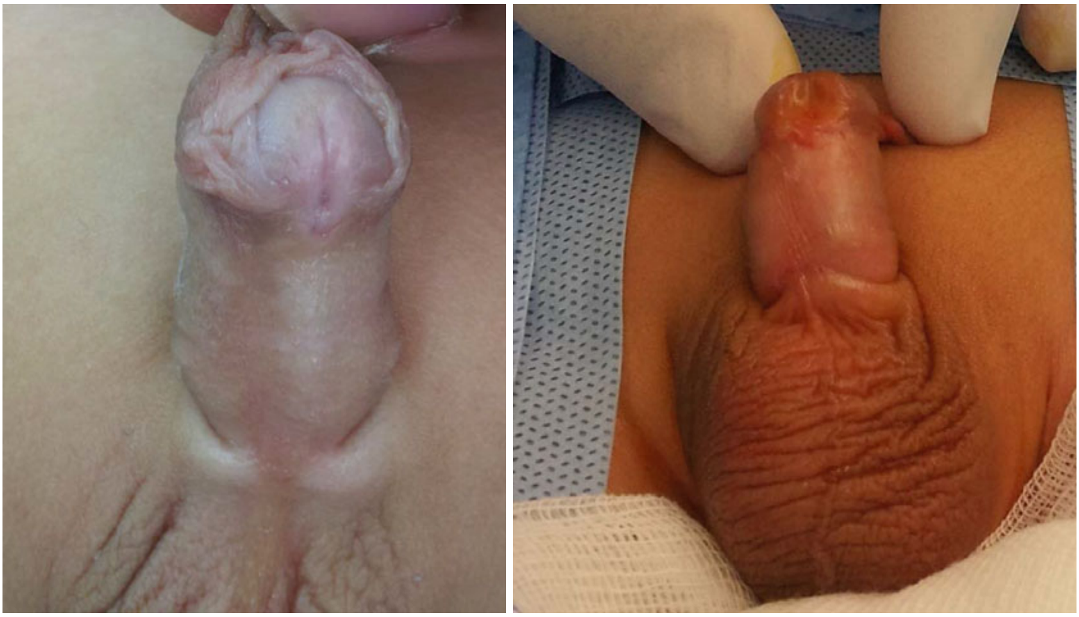
- There are several classifications for hypospadias depending on the site of the meatus.
- One of the oldest classification was that proposed by Browne in 1938.
  - Glandular hypospadias (Figs. 21.17 and 21.18)
  - Coronal hypospadias (Figs. 21.19 and 21.20)
  - Subcoronal hypospadias (Figs. 21.21 and 21.22)
  - Distal penile hypospadias (Figs. 21.23 and 21.24)
  - Midshaft hypospadias (Figs. 21.25 and 21.26)
  - Proximal penile hypospadias (Figs. 21.27 and 21.28)
  - Penoscrotal (Figs. 21.29 and 21.30)
  - Perineal (Figs. 21.31 and 21.32)
- The most accepted and currently used classification is the one proposed by Barcat and modified by Duckett in 1996. He divided the different types of hypospadias into anterior (50 %), middle (30 %) and posterior (20 %) hypospadias.
- These are also sub classified according to the location of the meatus:
  - The anterior type:
    - Glandular
    - Coronal
    - Distal penile
  - The middle type:
    - Midshaft
    - Proximal penile
  - The posterior type:
    - Penoscrotal
    - Scrotal
    - Perineal
- The latest classification was proposed in 2003 and divides hypospadias into three types.
  - Glaular
  - Distal
  - Proximal
- The subcoronal hypospadias is the most common type.



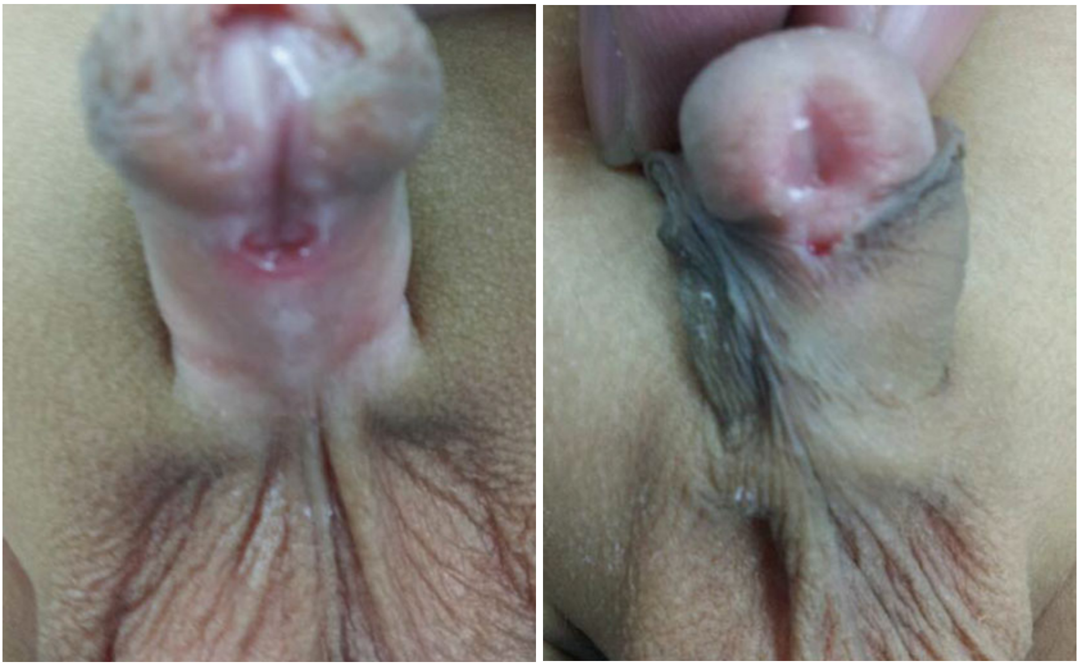
Figs. 21.17 and 21.18 Clinical photographs showing glanular hypospadias



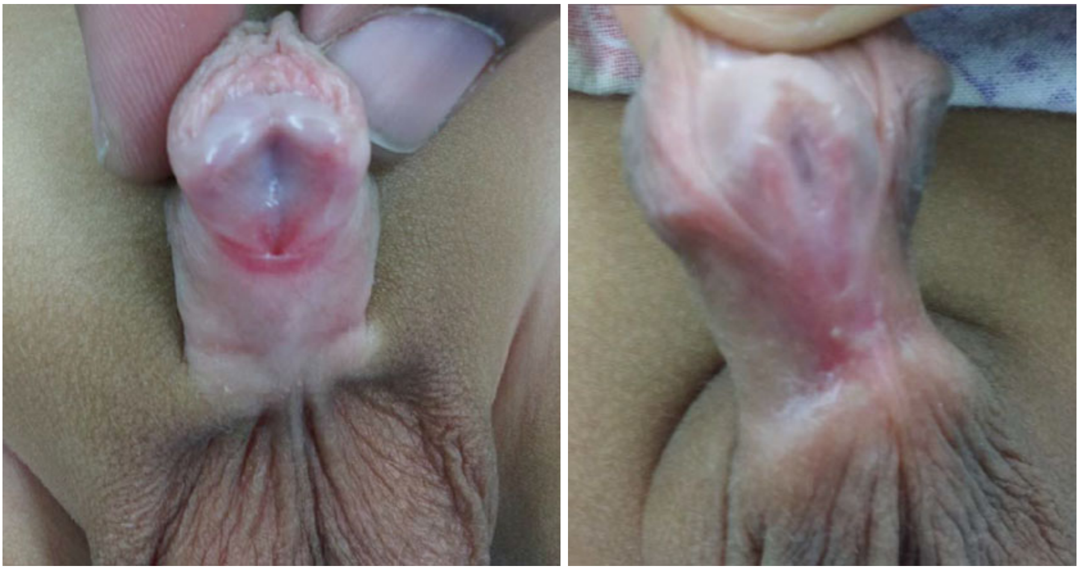
Figs. 21.19 and 20 Clinical photographs showing coronal hypospadias



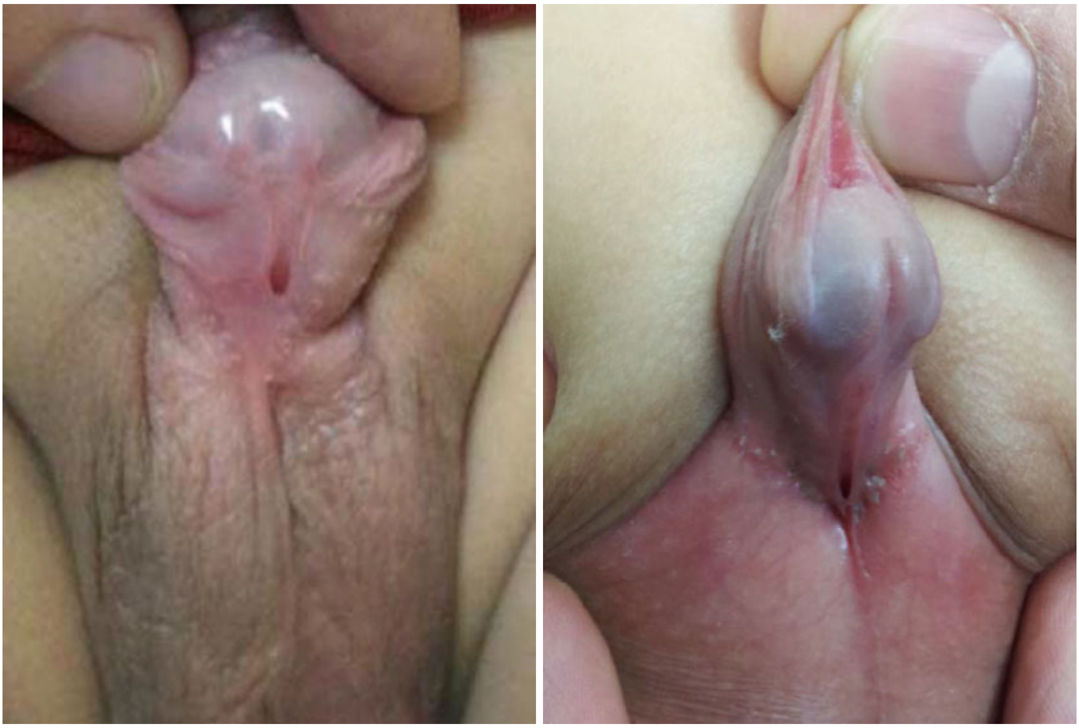
Figs. 21.21 and 21.22 A clinical photograph showing subcoronal hypospadias



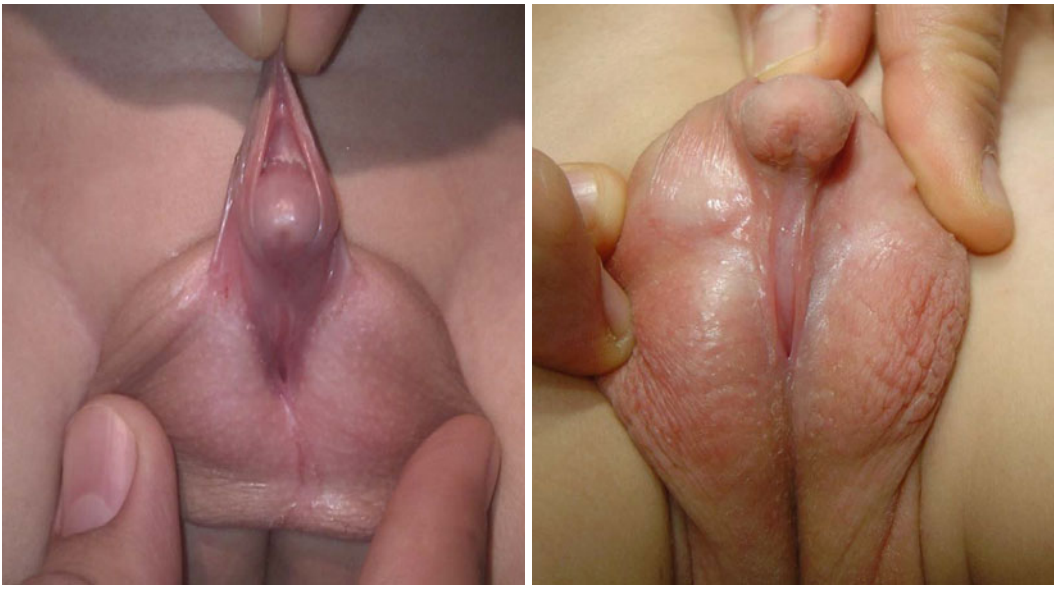
Figs. 21.23 and 21.24 Clinical photographs showing distal penile hypospadias



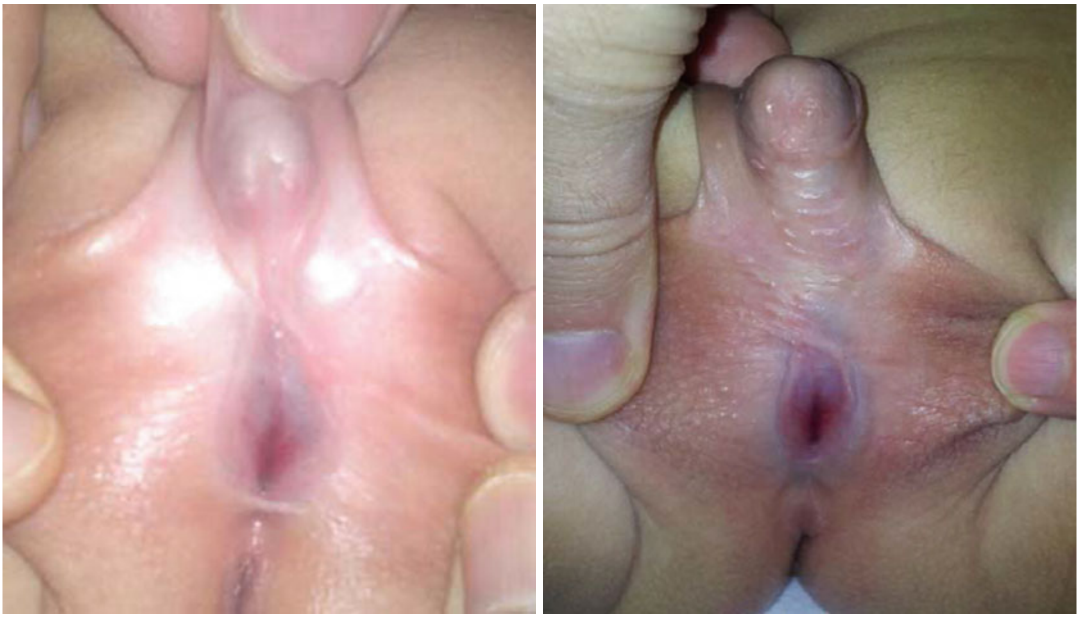
Figs. 21.25 and 21.26 Clinical photographs showing midshaft hypospadias



Figs. 21.27 and 21.28 Clinical photographs showing proximal hypospadias



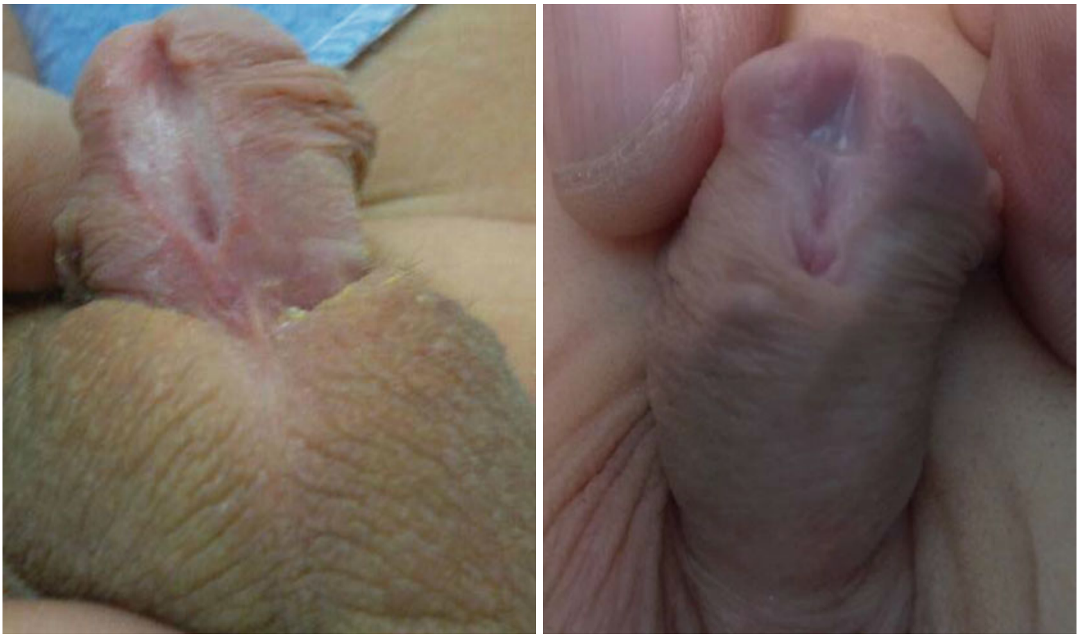
Figs. 21.29 and 21.30 Clinical photographs showing penoscrotal hypospadias



Figs. 21.31 and 21.32 Clinical photographs showing perineal hypospadias

21.7 Clinical Features of Hypospadias

- The urethral opening is ectopically located on the ventral aspect of the penis proximal to the tip of the glans penis (Figs. 21.33, 21.34, and 21.35).
- The urethral opening may be located as far down as in the scrotum or perineum.
- There is usually an associated glanular groove.



Figs. 21.33 and 21.34 Clinical photographs showing hypopsadias. Note the abnormal ectopic meatus on the ventral surface of the peis. Note also the glanular groove

The depth of this groove is variable.

- A dorsal hood of foreskin is present and the prepuce is incomplete ventrally ("hooded" foreskin).
- Rarely, the foreskin may be complete, and the hypospadias is revealed at the time of circumcision. This is called the mega meatus intact prepuce (MIP) variant of hypospadias (Figs. 21.36 and 21.37).
- The penis may have associated ventral shortening and curvature (chordee). This may be apparent during erection only and it is more commonly seen in patients with more proximal hypospadias (Figs. 21.38 and 21.39).

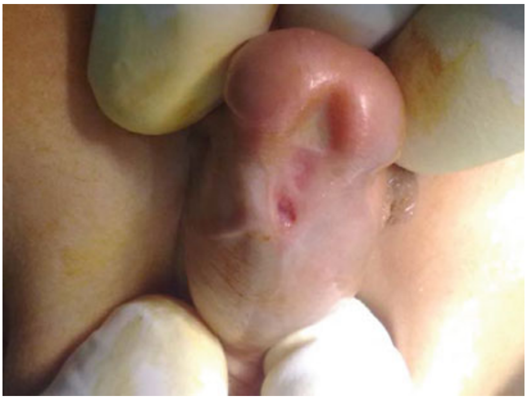
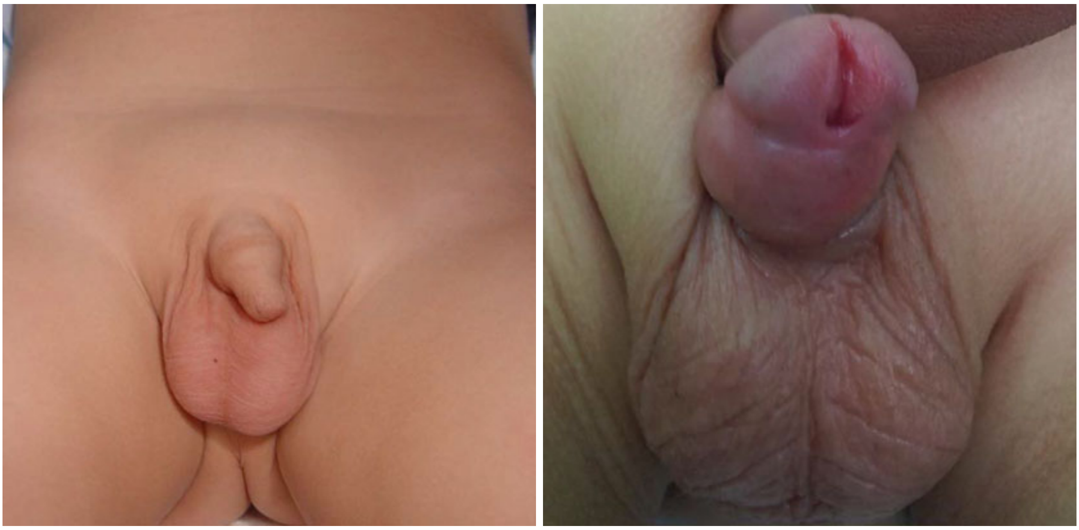
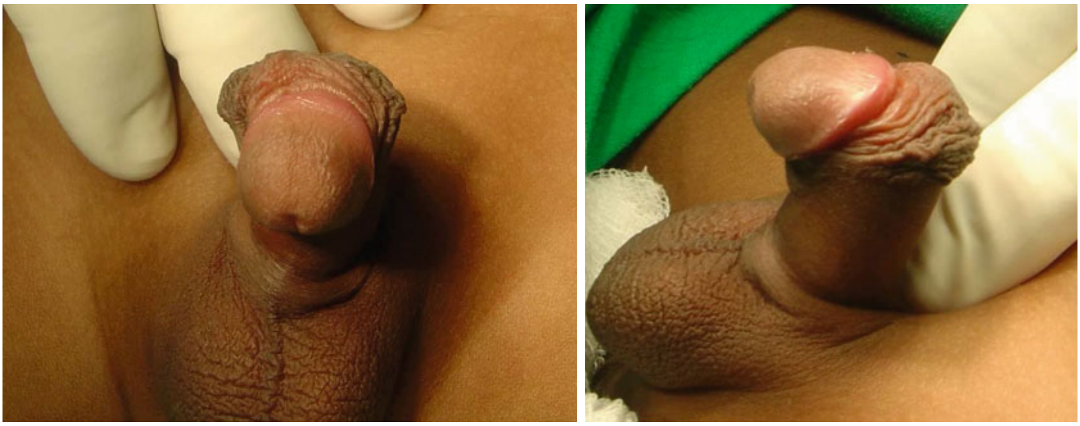


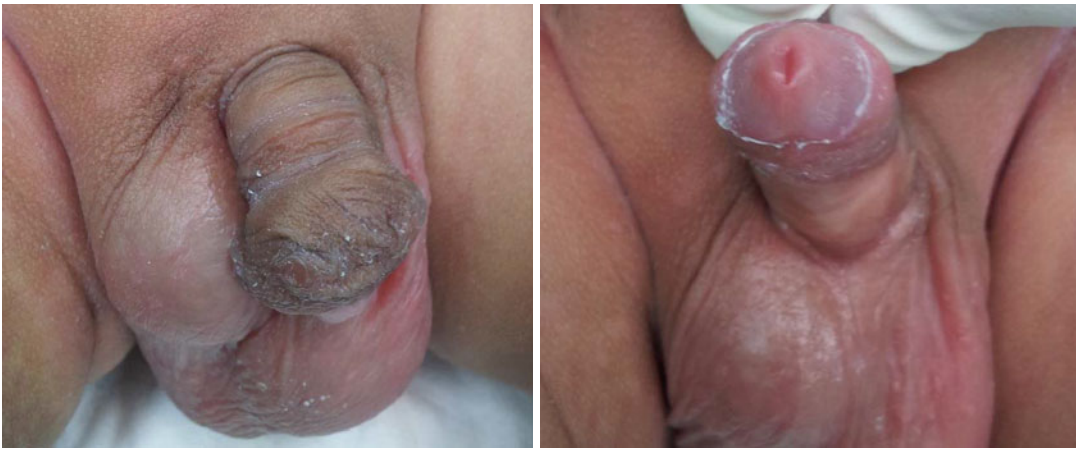
Fig. 21.35 A clinical photograph showing hypospadias. Note the deep glandular groove and the ectopic meatus on the ventral aspect of the penis



Figs. 21.36 and 21.37 Clinical photographs showing megameatus. Note the normal looking prepuce and also note the wide meatus



Figs. 21.38 and 21.39 Clinical photographs showing severe chordee associated with hypospadias

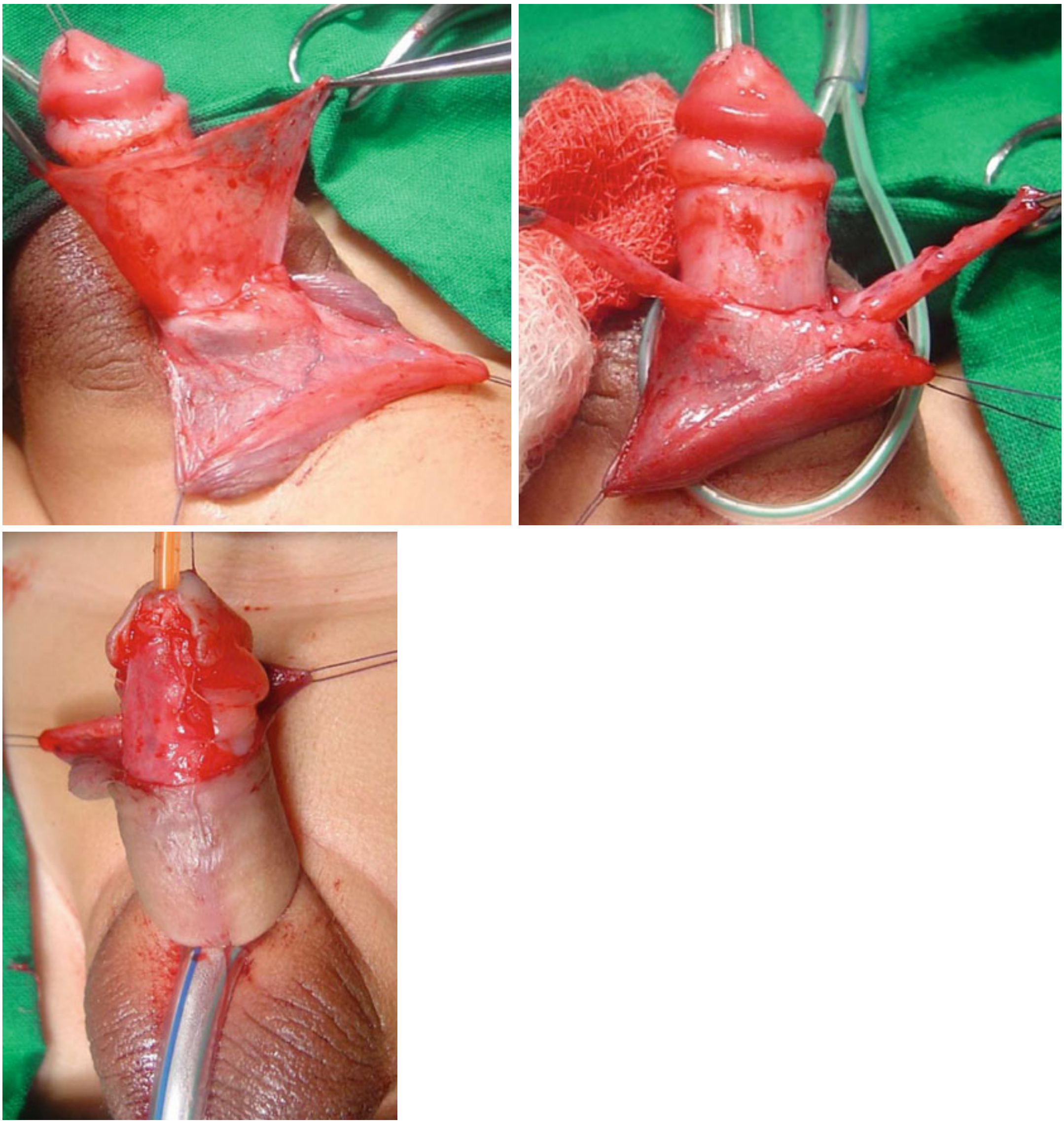


Figs. 21.40 and 21.41 Clinical photographs showing abnormal prepuce that is deficient ventrally but a normal looking meatus both in size and position

- Proximal hypospadias is commonly associated with a bifid scrotum and penoscrotal transposition.
- There may be an associated undescended testes which can be unilateral or bilateral.
- On rare occsions, the foreskin may appear abnormal resembling hypospadias but the meatus appears normal in position and site (Figs. 21.40 and 21.41).

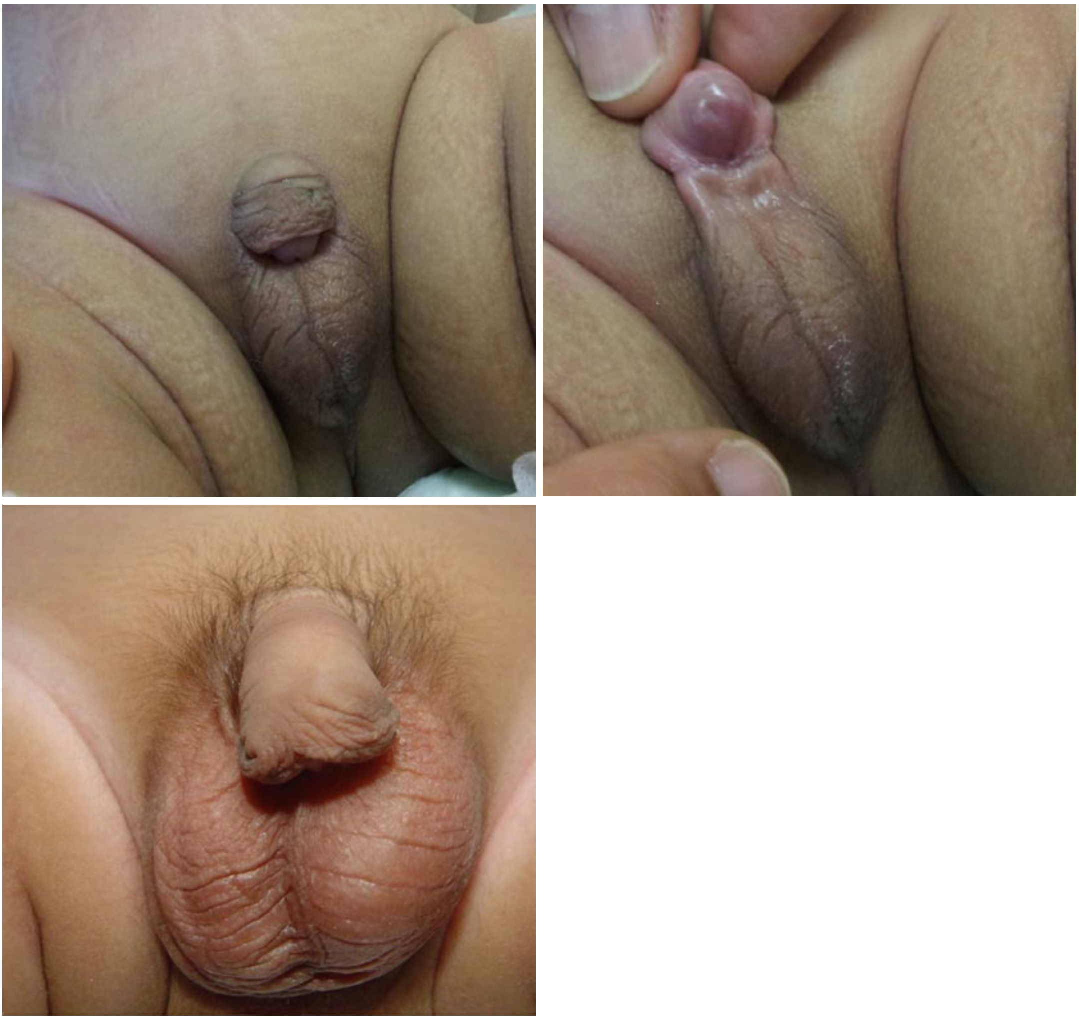
21.8 Treatment

- It is important to avoid circumscion in these children as the preputial skin is often used for grafting during hypospadias repair. The dartos flap of the preputial skin is dissected and used to protect the repair either as a single or double layers. This was shown to decrease the rate of postoperative fistula formation. The preputial skin is sometimes used to cover the deficient skin ventrally as Byer's flaps (Figs. 21.42, 21.43, and 21.44).
- Currently, most cases of hypospadias are repaired in the first 18 months of life and in a single stage (usually between 6 and 18 months of age.
- Hypospadias and hypospadias repair is known to be associated with significant psychological effect and to decrease this effect, repair of hypospadias is currently done at an earlier age group (6–18 months). This is known to have an improved emotional and psychological result.
- Repair of mild degrees of hypospadias is mainly for cosmetic reasons as they have little effect on function except for the direction of the urinary stream.
- The aim from the surgical repair is to have a penis that has an acceptable appearance, enable the patient to void normally and suitable for sexual intercourse in the future
- Hormonal therapy (Figs. 21.45, 21.46, and 21.47):
  - Hormonal therapy has been used as an adjuvant for infants with small phallic size.
  - The aim is to increase the length and width of the penis.
  - Testosterone injections or creams can be used.
- The recommended testosterone injection dose (long acting testosterone) is about 2 mg/kg/dose. This is given once every 3 weeks and can be repeated to a maximum of three doses.
- Human chorionic gonadotropin (HCG) injections, have been used also to promote penile growth.



Figs. 21.42, 21.43, and 21.44 Clinical intraoperative photographs showing the use of Dartos flaps as a single or double to protect the hypospadias repair

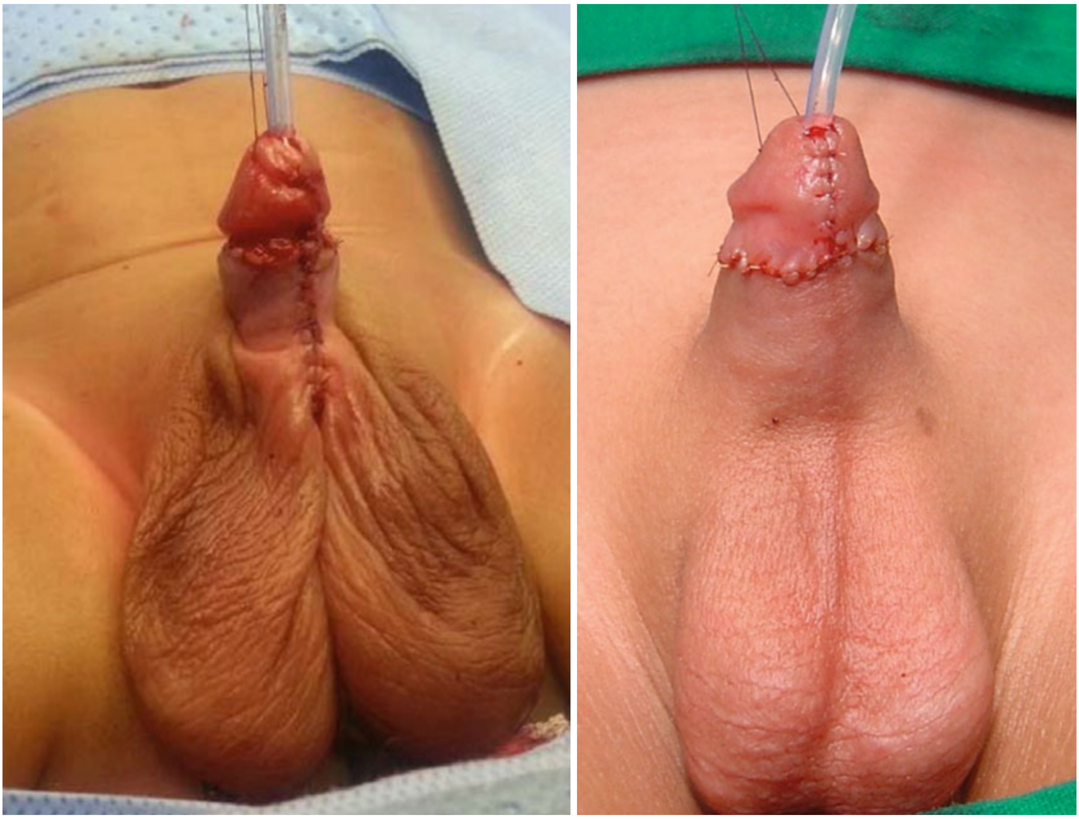
- The treatment of hypospadias is surgical repair, not only for functional reasons but also for cosmetic reasons.
- Hypospadias repair is generally performed as a single-stage procedure.
- A staged hypospadias repair is preferable in those with excessive chordee, and a small phallic size.
- The chordee is repaired during the first stage, and the urethroplasty and glansplasty are repaired after the first stage has completely healed.
- Hypospadias repair is done under general anesthesia, most often supplemented by a nerve block to the penis or a caudal block in order to reduce the general anesthesia needed,



Figs. 21.45, 21.46, and 21.47 Clinical photographs show in hypospadias before and after long acting testesterone injection. Note the increase in both the length and width of the penis. Note also the appearance of pubic hair as a side effect of long acting testesterone

and to minimize discomfort and pain after surgery.

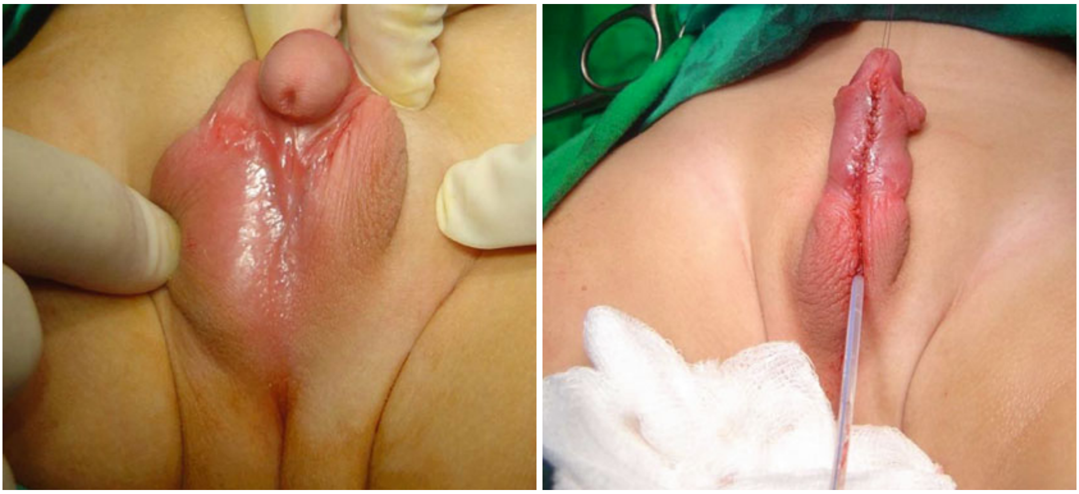
- The goals of surgical treatment of hypospadias are as follows (Figs. 21.48 and 21.49):
– To create a straight penis by repairing any curvature (orthoplasty)
– To create a urethra with its meatus at the tip of the penis (urethroplasty)
– To re-form the glans into a more natural conical configuration (glansplasty)
– To achieve cosmetically acceptable penile skin coverage
– To create a normal-appearing scrotum
- There are those who will not repair minor cases of hypospadias, in which the meatus is located near the tip of the glans.
- Hypospadias and hypospadias repair is known to be associated with significant psychological effect and to decrease this effect, repair of hypospadias is currently done at an earlier age group (6–18 months).
- This is known to have an improved emotional and psychological result.
- There are several surgical techniques to repair hypospadias depending on the site of urethral



Figs. 21.48 and 21.49 Clinical photographs showing posthypospadias repair

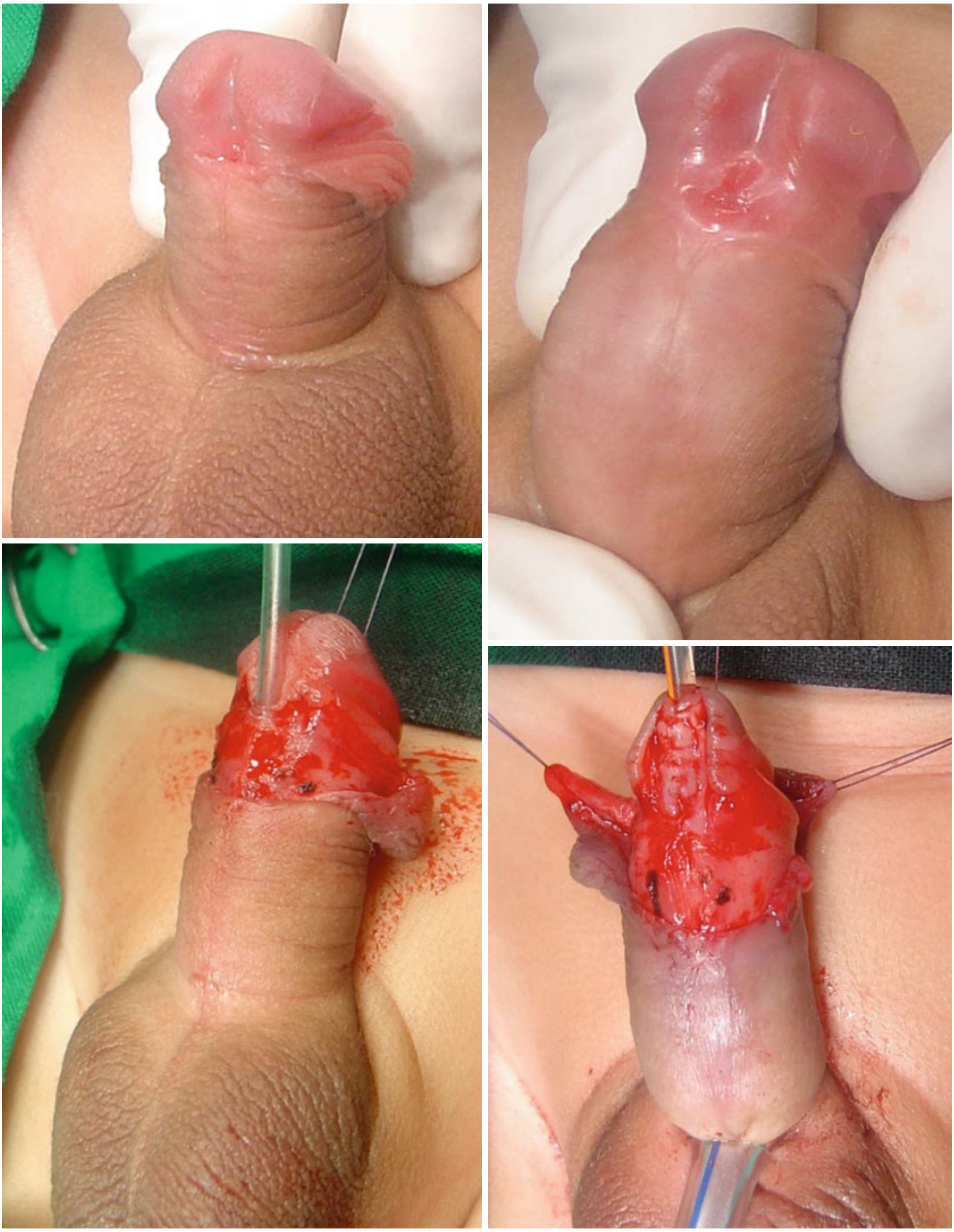
meatus and the presence or absence of chordee.

- Any degree of chordee should be corrected prior to urethroplasty.
- This may necessitates transection of the urethral plate in severe cases, precluding its use for urethroplasty (Figs. 21.50 and 21.51).
- Residual chordee is a known case of failure of urethroplasty. Add to this the bad cosmetic appearance.
- Glanular hypospadias:
  - This is commonly repaired using:
    - The MAGPI (Meatal Advancement Glanduloplasty Incorporated) procedure.
    - The DYG (The Double Y Glanuloplasty) procedure.
    - Others continue to use perimeatal-based flaps for urethroplasty ("flip-flap repair").
  - Very mild degree of glanular hypospadias can be repaired with meatoplasty.
  - There are those who advocate leaving a very mild degree of hypospadias without repair.
- Middle hypospadias:
  - There are several techniques to repair this type of hypospadias.
  - The TIP or Snodgrass urethroplasty (The tubularized incised plate urethroplasty) (Figs. 21.52, 21.53, 21.54, 21.55, 21.56, 21.57, 21.58, and 21.59):
- This is the commonest procedure used to repair anterior hypospadias (coronal, subcoronal, distal penile and midshaft hypospadias).
- A midline incision into the urethral plate widen it sufficiently for urethroplasty without stricture formation.
- This is suitable for cases without chordee or mild degrees of chordee.

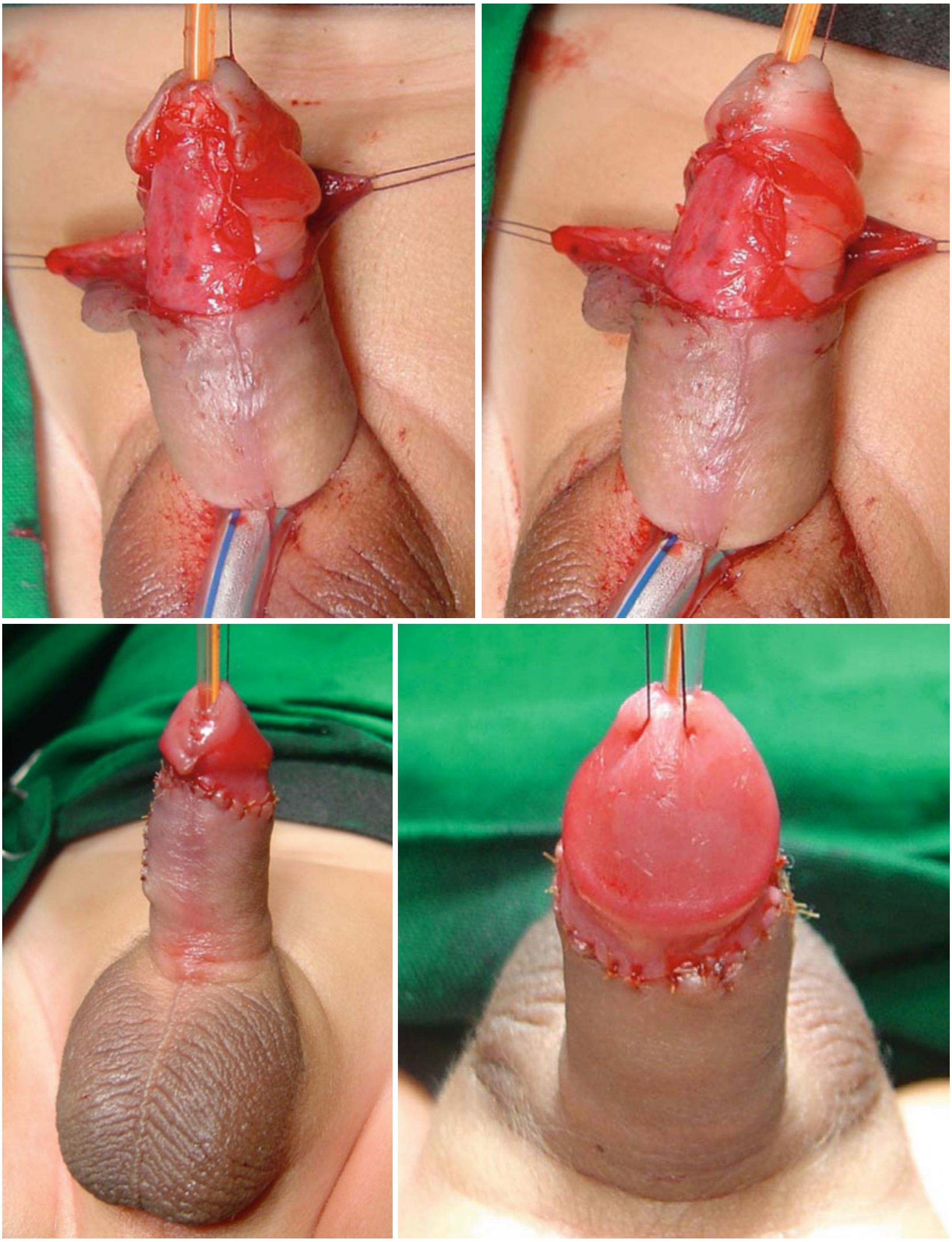


Figs. 21.50 and 21.51 Clinical photographs showing proxial hypospadias with severe chordee. Note the penile length after release of chordee and how straight it became

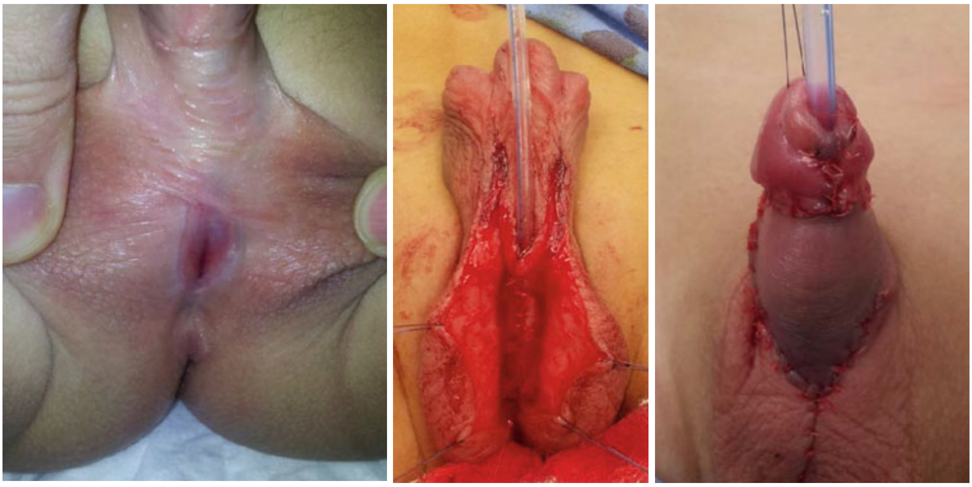
  - The Mathieu Technique:
    - This was modified and called The Slit-like adjusted Mathieu (SLAM) Technique.
    - The meatal-based flap technique of Mathieu was the most popular technique for distal hypospadias repair.
    - This technique is not commonly used now.
    - It is also not suitable for cases with chordee.
    - The major drawback of the original Mathieu technique is the final appearance of the meatus (a smiling meatus that is not very terminal).
  - The LABO technique (Lateral Based Onlay Flap):
    - The principle of this technique is to use the lateral penile skin as well as part of the prepuce to reconstruct the new urethra.
  - Lateral Based Flap:
    - The lateral based flap may be used in all types of proximal hypospadias.
    - This flap combines the advantages of meatal-based flap, and preputial pedicle flap techniques into one procedure without the need for an intervening anastomosis.
    - It is suitable for cases with chordee as it allows for extensive excision of ventral chordee and the urethral plate without damaging the flap.
  - Transverse Preputial Island Flap
  - Onlay Island Flap: The Onlay Island Flap is ideal for patients with proximal hypospadias without deep Chordee
- Posterior hypospadias (Figs. 21.60, 21.61, 21.62, 21.63, 21.64, and 21.65):
- There is less consensus regarding proximal hypospadias repair.
- Most of these cases are repaired using a two Stage repair.
- These as well as a small group of patients with severe proximal hypospadias, chordee, and a small phallus.
- Patients with recurrent hypospadias and fibrous unhealthy skin may benefit from a two-stage procedure.
- In the first stage, the chordee is excised completely and this confirmed by the use of the artificial erection test.
- The second stage of the procedure is carried out 6–12 months later.
- The tubularized incised plate (TIP) repair has become the most commonly used repair for both distal and midshaft hypospadias. This procedure can be used for all distal hypospa-



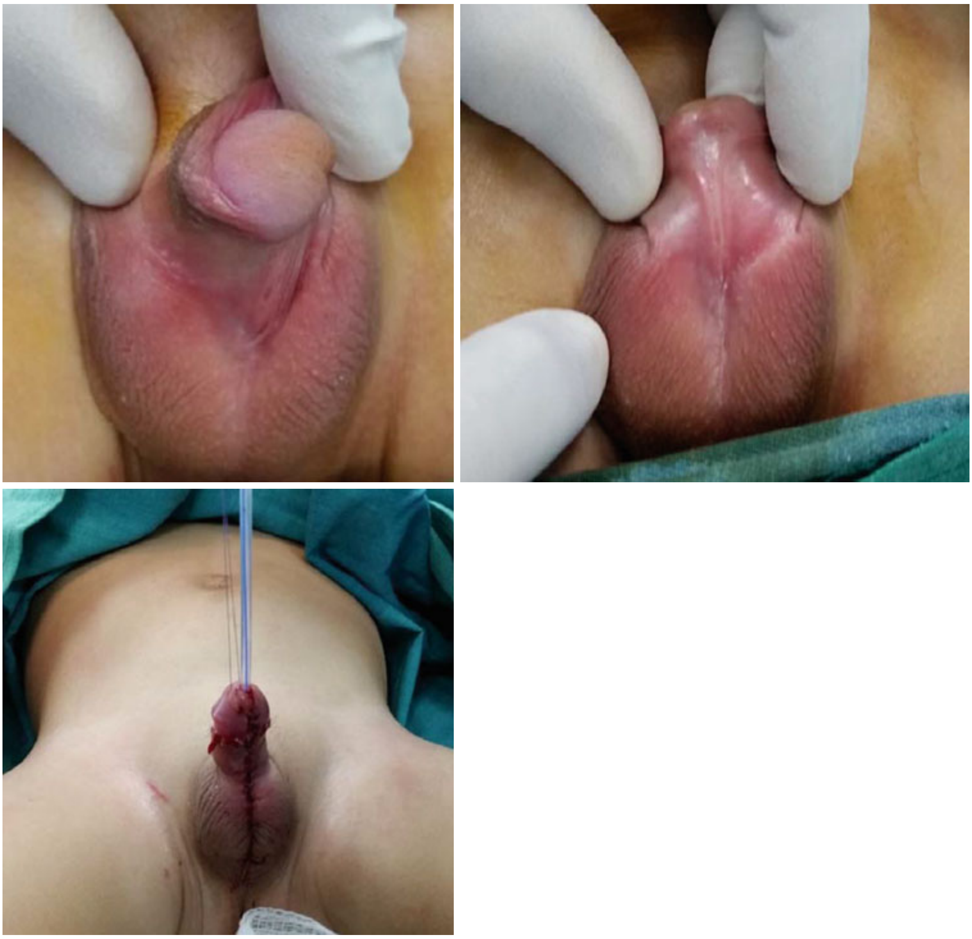
Figs. 21.52, 21.53, 21.54, 21.55, 21.56, 21.57, 21.58, and 21.59 Clinical photographs showing the steps of TIP procedure. The repair was reinforced with a double layer of dartos flaps



Figs. 21.52, 21.53, 21.54, 21.55, 21.56, 21.57, 21.58, and 21.59 (continued)



Figs. 21.60, 21.61, and 21.62 Clinical photograph showing the second stage repair of proximal hypospadias after release of chordee. The ventral skin defect was covered with a Byer's flaps



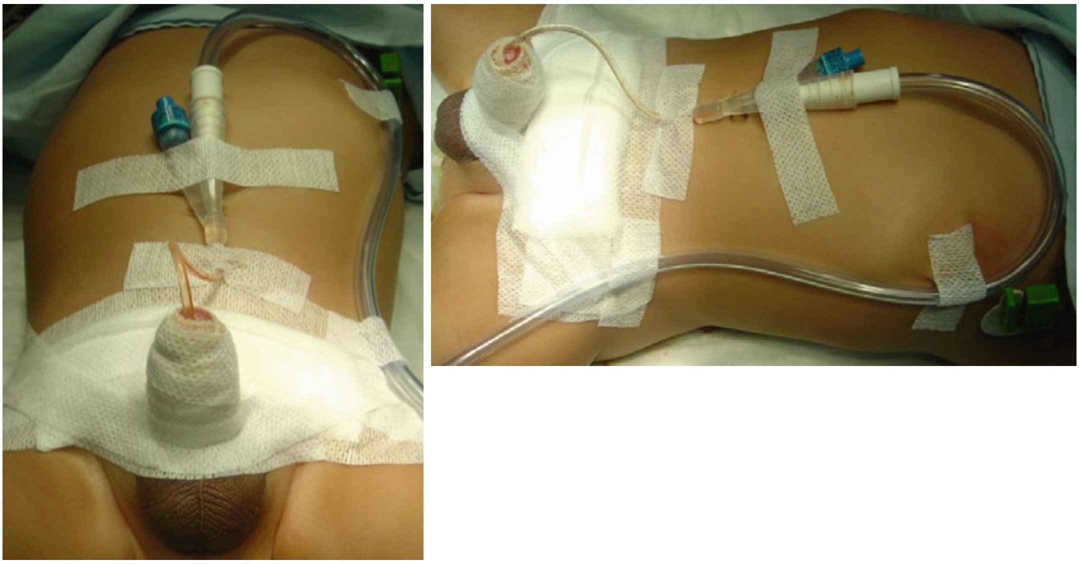
Figs. 21.63, 21.64, and 21.65 Clinical photographs showing proximal hypospadias without chordee that was repaired using TIP technique

dias repairs, with postoperative complications less than 10 % of cases. TIP repair can also be used to repair more proximal hypospadias when the penis is straight or has mild downward curvature.

- Various sutures have been used to repair of hypospadias.
- The buccal mucosa has been used for urethral grafting mainly for repeat repairs after unsuccessful surgery for hypospadias. This is specially so for patients who already had circumscion.
- There are several methods used to decrease the risk of fistula. One method is to increase the layers of tissue between the urethra and overlying skin using dartos flaps either single or double flaps.

21.9 Urinary Diversion

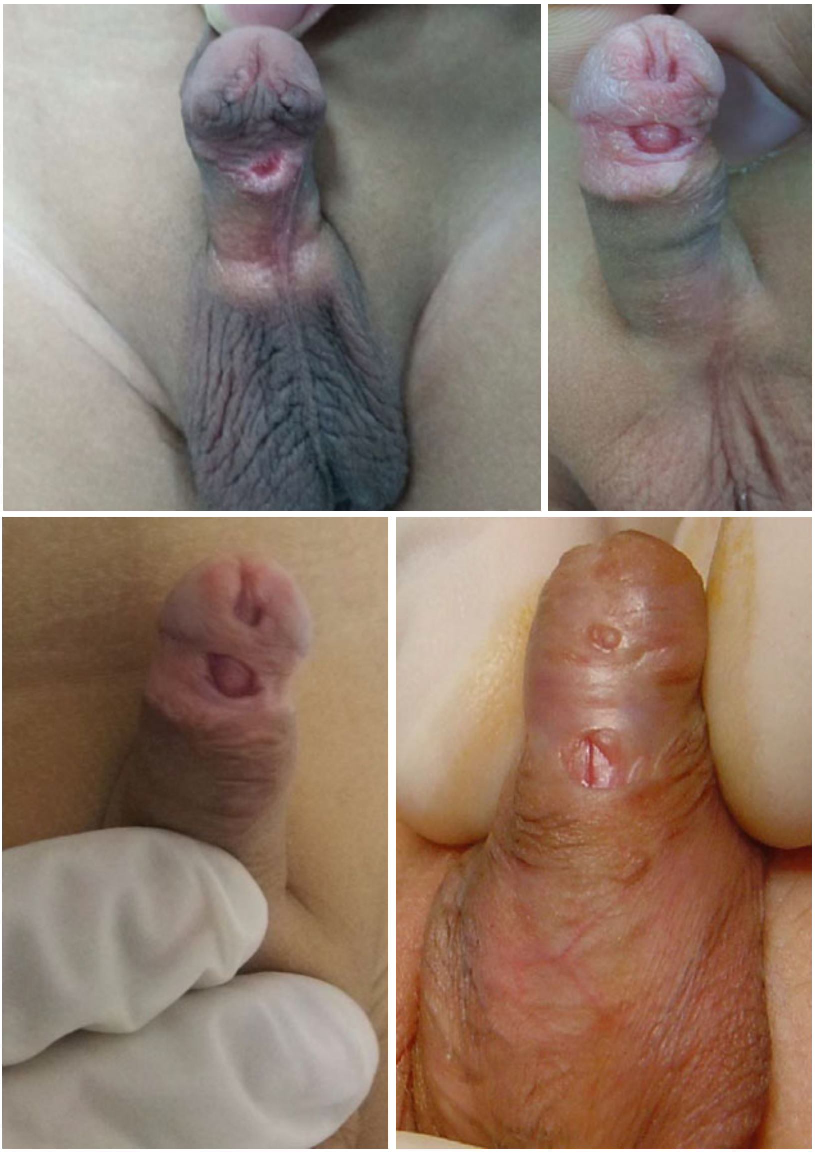
- The use of postoperative urinary diversion is still controversial.
- The importance of urinary diversion for preventing postoperative complications is not clear.
- There those who do not use routine urinary diversion while others prefer routine urinary diversion for all cases of hypospadias.
- Postoperative urinary diversion is performed to prevent urination against the newly created urethra.
- This is supposed to support wound healing.
- The use of urinary diversion restrict the activity of the child and may necessitates prolonged hospitalization especially those with a suprapubic urinary diversion.
- There are three different types of urinary diversion (Figs. 21.66 and 21.67):
  - Suprapubic urinary diversion (cistofix)
  - Transurethral urinary diversion with a balloon catheter (Foley’s catheter)
  - Transurethral urinary diversion with a “dripping stent”, which drains the bladder on a diaper.
- The duration of catheter drainage is variable ranging from 5 to 10 days depending on the extent of repair.
- Catheter drainage is also valuable in eliminating the possibility of acute urinary retention as this makes postoperative catheterization difficult and potentially harmful.



Figs. 21.66 and 21.67 A clinical photograph showing dressing and urinary diversion with a Foley’s catheter following repair of hypospadias

21.10 Postoperative Complications

- Repair of hypospadias is known to be associated with complications.
- Repair of the more proximal hypospadias are known to be associated with a greater incidence of complications.
- Immediate postoperative complications:
  - Local edema
  - Bruising
  - Postoperative bleeding and hematoma formation
  - Glans dehiscence
  - Wound dehiscence
  - Flap or graft necrosis
  - Urinary tract infections
  - Urinary tract obstruction
  - Catheter blockage
  - Infection is a rare complication of hypospadias repair



Figs. 21.68, 21.69, 21.70, and 21.71 Clinical photographs showing urethral fistulae following repair of hypospadias

- Long-term complications:
  - Urethrocutaneous fistula (Figs. 21.68, 21.69, 21.70, and 21.71):
- A fistula is an unwanted opening through the skin along the course of the urethra, and can result in urinary leakage or an abnormal stream.
- This is one of the common complications of hypospadias repair and a major concern.
- The incidence of fistula is variable and depends on the type of hypospadias and the repair used.
- Generally, the rate of fistula formation is less than 10 % for most single-stage repairs (5–10 %).
- This however rises with the severity of hypospadias, approaching 40 % with complex more proximal hypospadias.
- There are reports of spontaneous closure of fistula but this extremely rare.
- Fistulas are repaired by using a multilayered closure with local skin flaps 6 months after the initial repair.
- After repair, fistulas recur in approximately 10 % of patients.

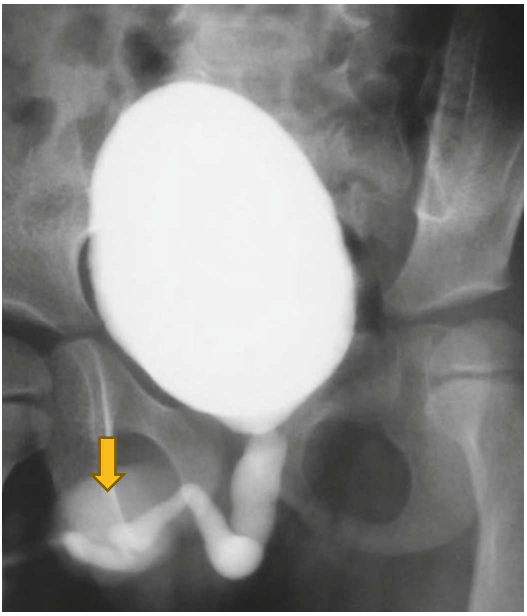
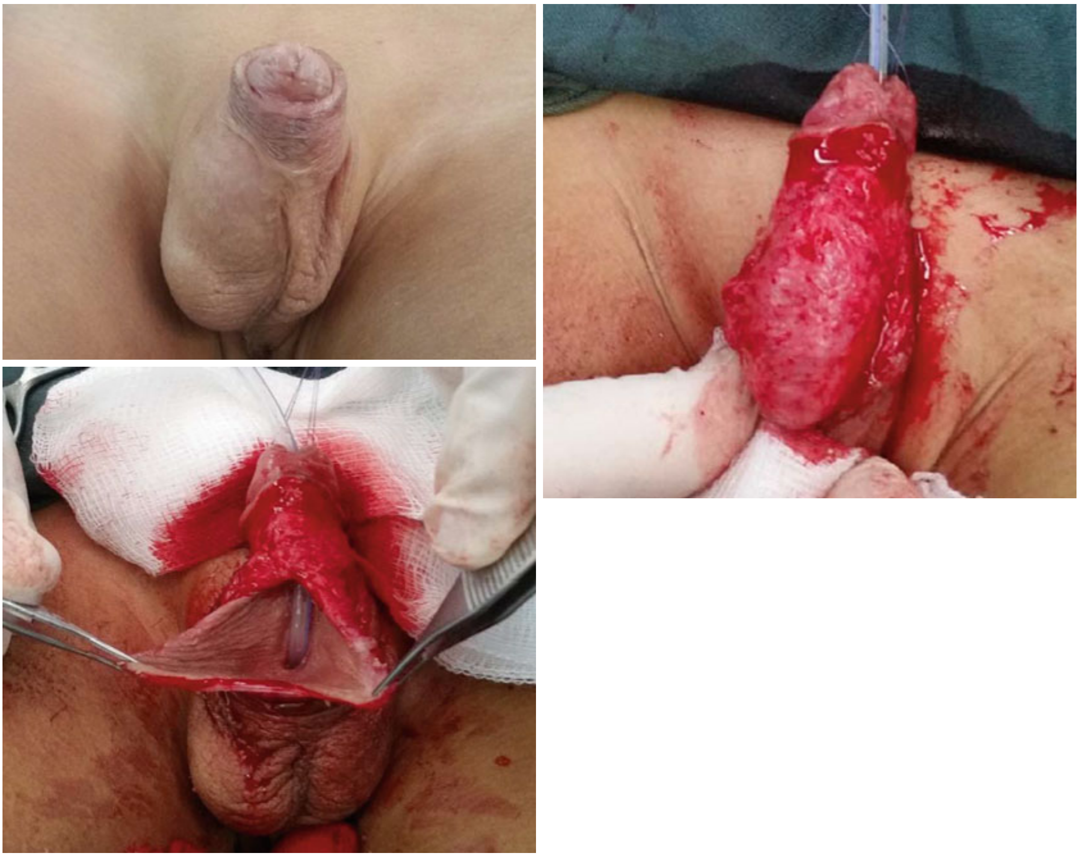


Fig. 21.72 A micurating cystourethrogram showing urethral stricture following repair of hypospadias

  - Meatal stenosis (7–15 %):
    - Another common complication of hypospadias is narrowing of the urethral meatus.
    - This may be cured with urethral dilatation or meatoplasty.
  - Urethral strictures (Fig. 21.72):
- These are long-term complication of hypospadias repair.
- A stricture is a narrowing of the urethra severe enough to obstruct flow.
- Dilatation is not effective in treating these strictures.
- These are generally repaired operatively and may require incision, excision with reanastomosis, or patching with a graft or pedicle skin flap.
  - Urethral diverticula (Figs. 21.73, 21.74, and 21.75):
- A urethral diverticulum is an “outpocketing” of the lining of the urethra which interferes with urinary flow and may result in post-urination leakage.
- This lead to ballooning of the urethra while voiding.
- Urethral diverticulum is also a cause of post void drippling of urine.
- It also causes recurrent urinary tract infection.
- There is usually an associated distal stricture which causes outflow obstruction.
- Diverticula can also form in the absence of distal obstruction and are generally associated with graft- or flap-type hypospadias repairs, which lack the subcutaneous and muscular support of native urethral tissue.
- The treatment is surgical excision of the diverticulum, the redundant urethral tissue and tapering of the urethra over a Foley’s catheter.
  - Hairy urethra:
    - Hair-bearing skin should be avoided in hypospadias repair.
    - The use of hair- bearing skin will lead to hairy urethra which is known to be problematic and can result in repeated urinary tract infection or stone formation.



Figs. 21.73, 21.74, and 21.75 Clinical and intraoperative photographs showing urethral diverticulum following repair of hypospadias. Note the diverticulum full of urine. It also causes postvoid driplling of urine

  - The treatment is cystoscopic depilation using a laser or cautery device.
  - In severe cases, the hair-bearing skin can be excised and a repeat hypospadias is done.
- Rarely, hypospadias is associated with mild degrees of erectile dysfunction. This is more seen in those with more proximal hypospadias repairs.
- Scarring is usually seen in patients following hypospadias repair. This is seen more in patient who underwent repeated attempts of hypospadias repair.
- Penile curvature is sometimes seen following hypospadias repair.
- Deviated penis (Fig. 21.76):

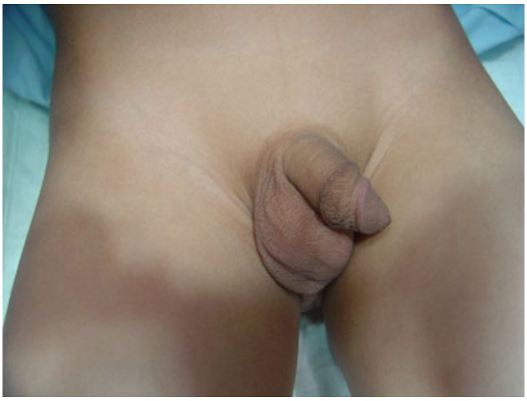


Fig. 21.76 A clinical photograph showing penile deviation following repair of hypospadias

- This can be seen following urethroplasty where the penis deviates to one side.
- The degree of deviation is variable.
- Mild degrees of deviation can be treated conservatively while those with severe degrees need correction.
- This can be achieved with plication technique.

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22 Male Circumcision

22.1 Introduction

- Male circumcision is derived from Latin *circumcidere*, meaning "to cut around".
- It is defined as the surgical removal of the foreskin (prepuce) from the human penis (Fig. 22.1).
- The origin of male circumcision is not known with certainty.
- The oldest documentary evidence for circumcision comes from ancient Egypt.
- It is part of religious law in Judaism and is an established practice in Islam, Coptic Christianity and the Ethiopian Orthodox Church.
- The practice and frequency of circumcision is different worldwide.
- Circumcision is one of the world's most widely performed procedures.
- The frequency of circumcision varies worldwide depending on geographic location, religious affiliation, and socioeconomic classification.
- Approximately one-third of males worldwide are circumcised, most often for religious or cultural reasons.
- The procedure is most prevalent in the Muslim world and Israel (where it is near-universal as a religious obligation), the United States and parts of Southeast Asia and Africa.
- Almost 70 % of circumcised children are Muslim.
- Circumcision is relatively rare in Europe, Latin America, parts of Southern Africa and most of Asia.
- Circumcision is most prevalent in:
  - The Muslim world
  - Israel
  - South Korea
  - The United States of America
  - Parts of Southeast Asia and Africa
- Circumcision is relatively rare in Europe, Latin America, parts of Southern Africa and Oceania and most of Asia.
- Non-religious circumcision in Asia, outside of the Republic of Korea and the Philippines, is fairly rare.

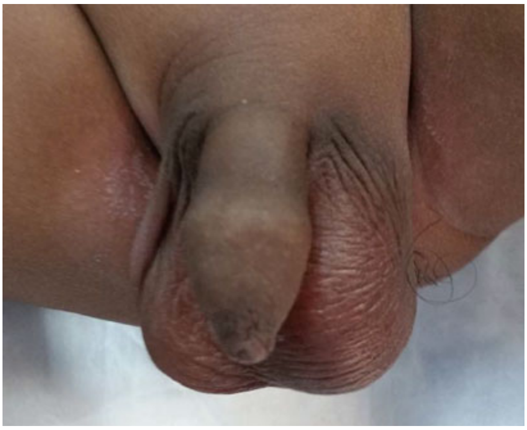

Fig. 22.1 A clinical photograph showing an uncircumcised infant

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A.H. Al-Salem, *An Illustrated Guide to Pediatric Urology*, DOI 10.1007/978-3-319-44182-5_22

- The prevalence of circumcision is generally low (<20 %) across Europe.
- The estimated prevalence of circumcision for individual countries is as follows:
  - Taiwan 9 %
  - Australia 58.7 %
  - The United States 75 %
  - Canada 30 %
  - In Africa, the prevalence varies from less than 20 % in some southern African countries to near universal in North and West Africa.
- In the United States of America, neonatal circumcision rates are different among racial and ethnic groups:
  - 81 % in whites
  - 65 % in African-Americans
  - 54 % in Hispanics
- Circumcision is performed by general practitioners, family physicians, general surgeons, urologist, pediatric surgeons, pediatric urologist, plastic surgeons, pediatricians and obstetricians.
- In the United States of America, approximately 70 % of obstetricians, 60 % of family practitioners, and 35 % of pediatricians practice newborn circumcision.
- In some countries, circumcision is also performed by nurses, midwives and non-professional not well trained persons.
- The procedure is most often performed on neonates and children for religious and cultural reasons.
- In other cases, circumcision is performed to treat or prevent complications. These include (Figs. 22.2 and 22.3):
  - Pathological phimosis and paraphimosis
  - Refractory balanoposthitis
  - Chronic urinary tract infections (UTIs)
  - Part of the corrective treatment of hypospadias, epispadias and chordee and ambiguous genitalia.
- Circumcision is associated with reduced rates of HPV related cancer and risk of both UTIs and penile cancer.
- It must be emphasized that circumcision does not appear to have a negative impact on sexual function.

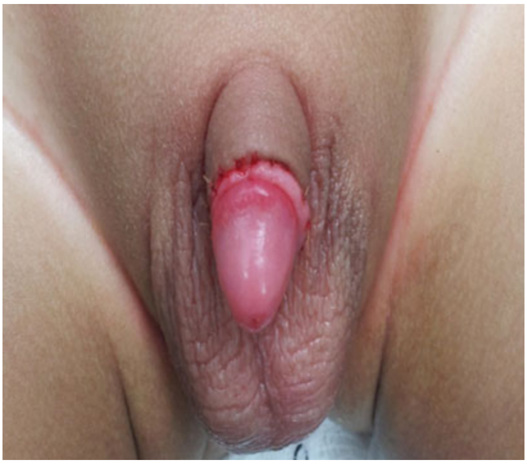


Fig. 22.2 A clinical photograph of a child following formal surgical circumcision

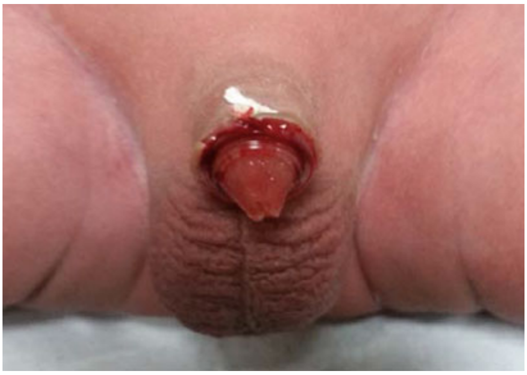


Fig. 22.3 A clinical photograph showing an infant following plastibel circumcision

- It was found that the benefits of circumcision outweigh the risks.
- This was supported by the fact that “Over their lifetime, half of uncircumcised males will require treatment for a medical condition associated with retention of the foreskin.”
- Others consider elective neonatal and child circumcision as having no benefit and significant risks to having a modest health benefit that outweighs small risks.
- Routine circumcision is not recommended by many medical organizations.
- The World Health Organization (WHO) recommends circumcision for parts of Africa with high rates of HIV as part of a comprehensive

HIV program. Evidence supports that male circumcision reduces the risk of HIV infection among heterosexual men.
- There are several techniques used in neonatal circumcision.
- The three most common devices used to date are:
  - The Gomco clamp (67 %)
  - The Plastibel device (19 %)
  - The Mogen clamp (10 %).
- Both the Gomco clamp and the Mogen clamp are excellent instruments for infants but should not be used in toddlers who weigh more than 5 kg because of an increased risk of bleeding.
- Cosmetic results are excellent with any of these devices if they are used correctly.
- The bone cutter is rarely used now.
- Plastibel circumcision can be used safely in children up to 10 kg under local anesthesia.
- Plastibel circumcision induces tissue necrosis by means of suture compression of the foreskin over a plastic ring that protects the glans. The skin sloughs off in 5–7 days, and the ring separates spontaneously.
- Plastibel circumcision is not without complications which include:
  - Bleeding
  - Failure of the plastibel to fall and needs to be removed manually or cut
  - Migration of the plastibel backward to the shaft and the plastibel needs to be cut
  - The use of improper size of plastibel can lead to incomplete circumcision.
- Circumcision is not without complications and have been reported to have a median complication rate of 1.5 % for newborns and 6 % for older children.
- These complication rates are higher when the procedure is performed by an inexperienced doctor. These complications include:
  - Bleeding
  - Infection
  - Removal of either too much or too little foreskin
  - A more serious complication is cutting part or whole glans penis
  - Iatrogenic hypospadias (urethral fistula)

22.2 Anatomy and Pathophysiology

- The prepuce (foreskin) is formed as a result of folding of the penile skin on itself at the level of the corona.
- This folded foreskin covers the glans penis.
- The corona is the grove that separate the shaft of the penis from the glans.
- The glans is covered with smooth hairless skin.
- The subcutaneous connective tissue of the penis and scrotum has a distinct layer with abundant smooth muscle called the dartos fascia.
- This layer continues into the perineum and fuses with the superficial perineal (Colle’s) fascia.
- In the penis, the dartos fascia is loosely attached to the skin and deep penile (Buck’s) fascia and contains the superficial arteries, veins, and nerves of the penis.
- The prepuce that covers the glans penis, is lined up by two layers, an external keratinized layer and an internal mucosal layer.
- This creates a pouch between these two linings.
- The pouch thus created can collect desquamated epithelial cells forming the so-called keratin pearls in infants and toddlers.
- In adolescence, cellular debris and local secretions collect in the form of smegma if the penis is not cleaned regularly.
- These secretions of the prepuce provides protection to the glans from dryness and keratinization.
- The nerve supply of the prepuce is from the dorsal nerve of the penis and branches of the perineal nerve. The autonomic nerve supply is primarily from the pelvic plexus.
- Groups that oppose neonatal circumcision argue that:
  - The foreskin has specialized nerve endings that enhance sexual pleasure.
  - The foreskin has important functions, including natural protection of the glans penis.
  - Permanent externalization of the glans penis results in desensitization due to

keratinization of the glans that buries nerve endings deep into this structure.
- Smegma is formed by desquamated epithelial cells trapped between the glans penis and foreskin through a natural process that aids in the normal separation of the glans from the foreskin. It appear as a white, cheese like substance (smegma) and it is considered a normal finding that is not indicative of infection.

22.3 History of Circumcision

- Circumcision is the world's oldest surgical procedure.
- The origins of circumcision is not well known.
- Some have suggested that this procedure originated in Egypt some 15,000 years ago and that its practice later spread throughout the world during prehistoric human migrations.
- This was supported by the findings of Egyptian mummies and wall carvings discovered in the nineteenth century documenting some of the earliest records of circumcision dating this procedure to at least 6,000 years BC.
- However, other authors believe that circumcision developed independently in different cultures.
- Columbus on his arrival to the New World found that many of the natives were already circumcised.
- In the lands south and east of the Mediterranean, starting with Sudan and Ethiopia, the procedure was practiced by the ancient Egyptians and the Semites, and then by the Jews and Muslims, with whom the practice travelled to and was adopted by the Bantu Africans.
- In Oceania, circumcision is practiced by the Australian Aborigines and Polynesians.
- Evidence suggests that circumcision was practiced in the Arabian Peninsula by the fourth millennium BCE, when the Sumerians and the Semites moved into the area that is modern-day Iraq.
- Many cultures have historically used circumcision:
  - For hygienic reasons
  - As a rite of passage to manhood
  - As a mark of cultural identity
  - As a ceremonial offering to the gods
- Ritual circumcisions in Middle Eastern cultures have been practiced for at least 3,000 years.
- Late in the nineteenth century, this ancient ritual evolved into routine medical practice influenced by reports that associated it with miraculous cures for hernias, paralysis, epilepsy, insanity, masturbation, headache, strabismus, rectal prolapse, hydrocephalus, clubfoot, asthma, enuresis, and gout.
- Circumcision is commonly practiced in the Jewish and Islamic faiths.
- Circumcision is very important to most branches of Judaism, with over 90% of adherents having the procedure performed as a religious obligation.
- In addition to proposing that circumcision was taken up by the Israelites purely as a religious mandate, scholars have suggested that Judaism's patriarchs and their followers adopted circumcision to make penile hygiene easier in hot, sandy climates; as a rite of passage into adulthood; or as a form of blood sacrifice
- Jewish circumcision is part of the *brit milah* ritual, to be performed by a specialist ritual circumciser (a *mohel*) on the eighth day of a newborn son's life (with certain exceptions for poor health).
- Jewish law requires that the circumcision leave the glans bare when the penis is flaccid.
- Circumcision (called *khitan*) is practiced nearly universally by Muslim males.
- Although it is not explicitly mentioned in the Quran, circumcision is considered essential to Islam, and it is nearly universally performed among Muslims.
- Circumcision is a tradition established by Islam's prophet Muhammad directly, and so its practice is considered a *Sunnah* (prophet's tradition) and is very important in Islam.
- The practice of circumcision spread across the Middle East, North Africa and Southern Europe with Islam.
- There is no agreement across the many Islamic communities about the age at which circumcision should be performed.

- It may be done from soon after birth up to about age 15; most often it is performed at around 6–7 years of age.
- The timing can correspond with the boy's completion of his recitation of the whole Quran, with a coming-of-age event such as taking on the responsibility of daily prayer.
- Circumcision is considered a major event and usually celebrated with an associated family or community.
- Christianity does not require circumcision; Christianity does not forbid it either.
- The Catholic Church currently maintains a neutral position on the practice of non-religious circumcision, although in 1442 it banned the practice of religious circumcision.
- Coptic Christians practice circumcision as a rite of passage.
- The Ethiopian Orthodox Church calls for circumcision, with near-universal prevalence among Orthodox men in Ethiopia.
- In South Africa, some Christian churches disapprove of the practice, while others require it of their members.
- In the Philippines, circumcision known as "tuli" is sometimes viewed as a rite of passage. About 93 % of Filipino men are circumcised.
- Certain African cultural groups, such as the Yoruba and Igbo of Nigeria, customarily circumcise their infant sons.
- The procedure is also practiced by some cultural groups or individual family lines in the Sudan, Zaire, Uganda and in southern Africa.
- For some of these groups, circumcision appears to be purely cultural, done with no particular religious significance or intention to distinguish members of a group.
- For others, circumcision might be done for purification, or it may be interpreted as a mark of subjugation.
- Among these groups, even when circumcision is done for reasons of tradition, it is often done in hospitals.
- It is not clear how many deaths and injuries result from traditional circumcisions which occur outside of hospitals.
- Routine neonatal circumcision has become a controversial issue in the past two decades as many of the previously accepted medical indications have come under considerable scrutiny.
- The first medical doctor to advocate for the adoption of circumcision, was the eminent English physician, Jonathan Hutchinson. In 1855, he published a study in which he compared the rate of contraction of venereal disease amongst the gentile and Jewish population of London. His study appeared to demonstrate that circumcised men were significantly less vulnerable to such disease.
- Circumcision was also employed as a means of discouraging masturbation. Circumcision was also recommended to prevent masturbation.
- In America, one of the first modern physicians to advocate circumcision was Lewis Sayre, a founder of the American Medical Association. In 1870, Sayre began using circumcision to prevent or as a cure for several array of medical problems and social ills. As a result of his publications and promotion, in both America and Great Britain, infant circumcision was near universally recommended.
- In 1949, Douglas Gairdner showed that the risks of circumcision outweighed the known benefits.
- In the 1970s, national medical associations in Australia and Canada issued recommendations against routine infant circumcision.
- The United States made similar statements in the 1970s, but stopped short of recommending against it—simply stating that it has no medical benefit.
- Subsequently, they have amended their policy statements several times. The current recommendation being that the benefits outweigh the risks, but they do not recommend it routinely.
- Because neonatal circumcision poses both potential benefits and risks and because the procedure is not necessary for a child's well-being, the American Academy of Pediatrics (AAP) Task Force on Circumcision in its latest policy statement in 1999 affirms that "existing scientific evidence demonstrates potential benefits of newborn male circumcision; however, these data are not sufficient to

recommend routine neonatal circumcision." As a consequence, parents should be appropriately counseled so that they can make an informed choice and decide whether a circumcision is in the best interest of their child.

- Worldwide, most legal jurisdictions do not have specific laws concerning the circumcision of males.
- Infant circumcision is considered legal under the existing laws in countries such as Australia, Canada, New Zealand, the United Kingdom, and the United States.
- A few countries have passed legislation on the procedure: Germany allows non-therapeutic circumcision under certain conditions, while routine neonatal circumcision is illegal in Finland, non-religious routine circumcision is illegal in South Africa and Sweden.
- In the 9th edition of the Encyclopedia Britannica published in 1876, discusses the practice of circumcision as a religious rite among Jews, Muslims, the ancient Egyptians and tribal peoples in various parts of the world.
- In 1910 the Encyclopedia Britannica changed the statement regarding circumcision: "This surgical operation, which is commonly prescribed for purely medical reasons, is also an initiation or religious ceremony among Jews and Muslims".
- An association between circumcision and reduced heterosexual HIV infection rates was suggested in 1986. To establish this, trials took place in South Africa, Kenya and Uganda and showed the circumcised group had a lower rate of HIV contraction than the control group.
- Subsequently, the World Health Organization promoted circumcision in high-risk populations as part of an overall program to reduce the spread of HIV.
- The Male Circumcision Clearinghouse website was formed in 2009 by WHO, UNAIDS, FHI and AVAC to provide current evidence-based guidance, information and resources to support the delivery of safe male circumcision services in countries that choose to scale up the procedure as one component of comprehensive HIV prevention services.

22.4 Pain Management

- It is well known that circumcision causes pain, and for neonates this pain may interfere with mother-infant interaction or cause other behavioral changes.
- To avoid this, pre and post circumcision analgesia is advocated.
- There are several methods to achieve this.
  - Paracetamol orally or suppository
  - Topical analgesic creams (EMLA cream which is a mixture of prilocaine and lidocaine)
  - Localized or regional nerve blocks (ring block and dorsal penile nerve block)
  - The ring block and dorsal penile nerve block (DPNB) are the most effective at reducing pain.
  - The ring block may be more effective than the DPNB.
  - The ring block and dorsal penile nerve block are more effective than EMLA cream.
- Non-pharmacological methods to reduce circumcision pain include:
  - The use of a comfortable, padded chair
  - The use of a sucrose or non-sucrose pacifier
- The American Academy of Pediatrics (AAP) states that such methods are insufficient alone and should be used to supplement more effective techniques.
- A quicker procedure to do circumcision reduces duration of pain.
- The use of the Mogen clamp was found to result in a shorter procedure time and less pain-induced stress than the use of the Gomco clamp or the Plastibel.
- Formal surgical circumcision in older children is done under general anesthesia. This can be supplemented with a caudal block to reduce postoperative pain.

22.5 Indications for Circumcision

- Circumcision is commonly performed for cultural, religious, or hygienic reasons.

- Medical indications for circumcision include:
  - Phimosis
  - Paraphimosis
  - Balanitis and posthitis
  - Recurrent urinary tract infection
  - Children who require clean, intermittent catheterization
  - Part of the repair of hypospadias, epispadias and ambiguous genitalia
- Phimosis:
  - Phimosis is a condition in which the distal prepuce cannot be retracted over the glans penis.
  - Severe phimosis can be demonstrated by bulging of the foreskin during micturition.
  - Phimosis causes chronic skin irritations, yeast infections, balanitis, posthitis, and the forceful retraction of the foreskin may result in paraphimosis.
  - Phimosis may cause pain and difficulty during micturition and may cause pain during sexual activity.
  - Acquired or pathological phimosis occurs as a result of:
    - Poor hygiene
    - Chronic or repeated episodes of balanoposthitis
    - Repetitive forceful retraction of the foreskin
    - Scaring from the skin disease balanitis xerotica obliterans (BXO)
    - Circumcision complication
  - Circumcision is the treatment for pathological phimosis.
- Paraphimosis:
  - Paraphimosis is the inability to reduce a retracted foreskin over the glans penis to its naturally occurring position.
  - Paraphimosis can result when parents or physicians forcibly retract the foreskin to clean the penis or attempt catheterization and do not return the foreskin to its original position.
  - Edema, tenderness, and erythema of the glans are seen, along with edema of the distal foreskin and flaccidity of the penile shaft proximal to the areas of paraphimosis.
  - Paraphimosis is a true urologic emergency and should be treated as soon as possible.
  - If not treated promptly, it can result in venous engorgement and edema of the glans and foreskin which, over time, progresses to arterial occlusion and the risk of ischemic loss of portions or the entire glans penis.
  - Paraphimosis is treated by manual reduction of the prepuce over the glans.
  - If manual reduction fails, a dorsal incision at the level of the constricting band releases the foreskin.
  - Circumcision should later be performed electively.
- Balanitis or posthitis:
  - Posthitis is an infection of the prepuce, whereas balanitis is an infection of the glans penis.
  - An inflammation of the glans penis and foreskin is called balanoposthitis
  - Balanitis and posthitis may be the result of poor hygiene.
  - Most cases occur in uncircumcised males, affecting 4–11 % of uncircumcised males.
  - The moist, warm space underneath the foreskin is thought to facilitate the growth of pathogens, particularly when hygiene is poor.
  - The infection is usually caused by mixed flora.
  - Yeasts, especially *Candida albicans*, are the most common penile infection
  - Trichomonal balanitis and candidal infections may be seen in sexually active teenagers.
  - Posthitis is characterized by erythema, swelling, warmth, and tenderness of the foreskin.
  - Balanitis is characterized by erythema, swelling, warmth, and tenderness of the glans penis.
  - A foul-smelling, thin, seropurulent exudate may be seen.
  - Both of these infections are treated with oral and topical antibiotics and warm baths.
  - Circumcision is a treatment option for refractory or recurrent balanoposthitis.

- Management of urinary tract infections:
  - A urinary tract infections affects parts of the urinary system including the urethra, bladder, and kidneys.
  - There is about a 1 % risk of UTIs in boys under 2 years of age, and the majority of incidents occur in the first year of life.
  - Urinary tract infections are more common in male neonates than in females.
  - There is an increased rate of urinary tract infections in uncircumcised males, especially in infants younger than 1 year.
  - A study of infants with UTIs showed that 75 % of those younger than 3 months were males and, of those, 95 % were uncircumcised.
  - There is good evidence that circumcision reduces the incidence of urinary tract infections in boys under 2 years of age.
  - Recommending routine circumcision in all newborn males is controversial and prevention of UTIs does not justify routine use of circumcision, however.
  - Circumcision is most likely to benefit boys who have a high risk of urinary tract infections due to anatomical defects, and may be used to treat recurrent UTIs. Circumcision may reduce the risk of urinary tract infections through a decrease in the bacteria population.
  - Some children are at increased risk for UTIs, such as children with neurogenic bladders who require clean, intermittent catheterization or children with poorly emptying urinary tracts. Circumcision in these patients will facilitate the procedure and reduce the risk of UTIs.
- Management of sexually transmitted diseases (STDs):
  - There is strong evidence that circumcision reduces the risk of HIV infection in heterosexual men in high-risk populations.
  - The finding that circumcision significantly reduces female-to-male HIV transmission in the HIV/AIDS epidemic sub-Saharan Africa prompted the World Health Organization (WHO) to recommend circumcision as an additional method of controlling the spread of HIV.
  - Circumcision is recommended as part of a comprehensive program for prevention of HIV transmission in areas with high endemic rates of HIV.
  - Evidence among heterosexual men in sub-Saharan Africa shows an absolute decrease in risk of 1.8 % which is a relative decrease of between 38 and 66 % over 2 years, and in this population studies rate it cost effective.
  - Whether it is of benefit in developed countries is undetermined.
  - Circumcision only provides partial protection from HIV and known methods should not replace HIV prevention.
  - There are several mechanisms proposed to explain the increased risk for STDs in uncircumcised males. These include:
    - A relatively nonkeratinized inner layer of the prepuce which increases its susceptibility to minor trauma during intercourse, allowing pathogens to penetrate through microscopic abrasions.
    - The warm microclimate created by the preputial pouch permits the microorganisms to thrive in the smegma that collects in this area.
    - The superficial skin layers of the penis contain Langerhans cells, which are targeted by HIV; removing the foreskin reduces the number of these cells.
    - When an uncircumcised penis is erect during intercourse, any small tears on the inner surface of the foreskin come into direct contact with the vaginal walls, providing a pathway for transmission.
  - A significant two- to sevenfold increased risk of genital syphilis and chancroid was reported in uncircumcised male patients.
  - Circumcision was found to be associated with lower rates of syphilis, chancroid and possibly genital herpes.
  - Circumcision reduced the incidence of HSV-2 (herpes simplex virus, type 2) infections by 28 %.

- Management of human papillomavirus and cervical cancer:
  - Human papilloma virus (HPV) can be oncogenic or nononcogenic.
  - Nononcogenic HPV (genotypes 6 and 11) causes genital warts in men and women.
  - Oncogenic HPV (genotypes 16, 18, 31, and 33) are responsible for the great majority of cervical, vulvar, vaginal, anal, and penile cancers.
  - Circumcision significantly reduces the risk of penile HPV infection in men and of cervical cancer in the female partners of male individuals who practice high-risk behaviors such as engaging in sexual activity with multiple partners.
  - Human papilloma virus (HPV) is the most common sexually transmitted infection, affecting both men and women. While most infections are asymptomatic and are cleared by the immune system, some types of the virus cause genital warts, and other types, if untreated, cause various forms of cancer, including cervical cancer and penile cancer.
  - Genital warts and cervical cancer are the two most common problems resulting from HPV.
  - Circumcised man are less likely to be infected with cancer-causing types of HPV.
  - Circumcision decreases the likelihood of multiple infections.
- Penile cancer:
  - Circumcision has a protective effect against the risks of penile cancer in men, and cervical cancer in the female sexual partners of heterosexual men.
  - Penile cancer is rare, with about 1 new case per 100,000 people per year in developed countries, and higher incidence rates per 100,000 in sub-Saharan Africa (for example, 1.6 in Zimbabwe, 2.7 in Uganda and 3.2 in Swaziland).
  - Penile cancer development can be detected in the carcinoma *in situ* (CIS) cancerous precursor stage and at the more advanced invasive squamous cell carcinoma stage.
  - Childhood or adolescent circumcision is associated with a reduced risk of invasive squamous cell carcinoma in particular.
  - There is an association between adult circumcision and an increased risk of invasive penile cancer; this is believed to be from men being circumcised as a treatment for penile cancer or a condition that is a precursor to cancer rather than a consequence of circumcision itself.
  - The most important factor associated with the development of penile cancer is an intact foreskin.
  - Penile cancer has been observed to be nearly eliminated in populations of males circumcised neonatally.
  - Jewish men (the great majority of them circumcised) rarely develop penile cancer.
  - The other known major risk factor associated with penile cancer is phimosis.
  - Circumcision completely eliminates these risks.

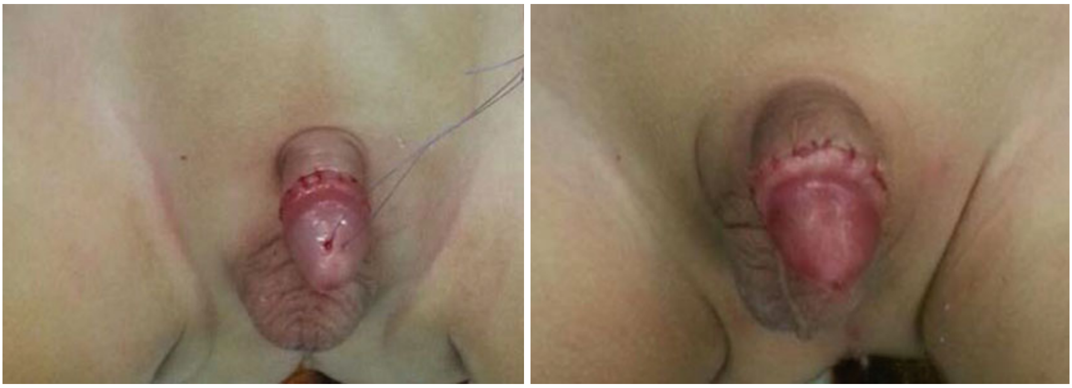
22.6 Contraindications to Circumcision

- Prematurity
- Chordee of the penis
- Curvature of the penis
- Hypospadias
- Epispadias
- Concealed or buried penis
- Micropenis
- Webbed penis
- Ambiguous genitalia
- Bleeding diatheses
- In those with chordee of the penis, curvature of the penis, micropenis, webbed penis and concealed or buried penis, circumcision is delayed and open classic surgical circumcision is performed.
- In those with Hypospadias, Epispadias and Ambiguous genitalia, circumcision is done as part of the corrective surgery of these anomalies.
- Bleeding diatheses are not absolute contraindications for circumcision, and circumcisions

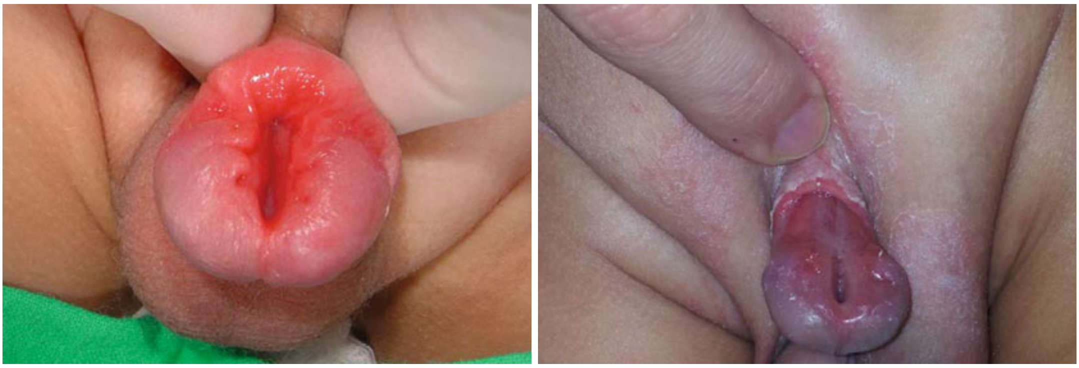
can be performed after preparation and treatment. The parents should be fully informed of the increased risks of complications.
- Circumcision is contraindicated in premature infants and those who are not clinically stable and in good health.
- A family history of hemophilia calls for a coagulation profile prior to circumcision.

22.7 Surgical Procedure

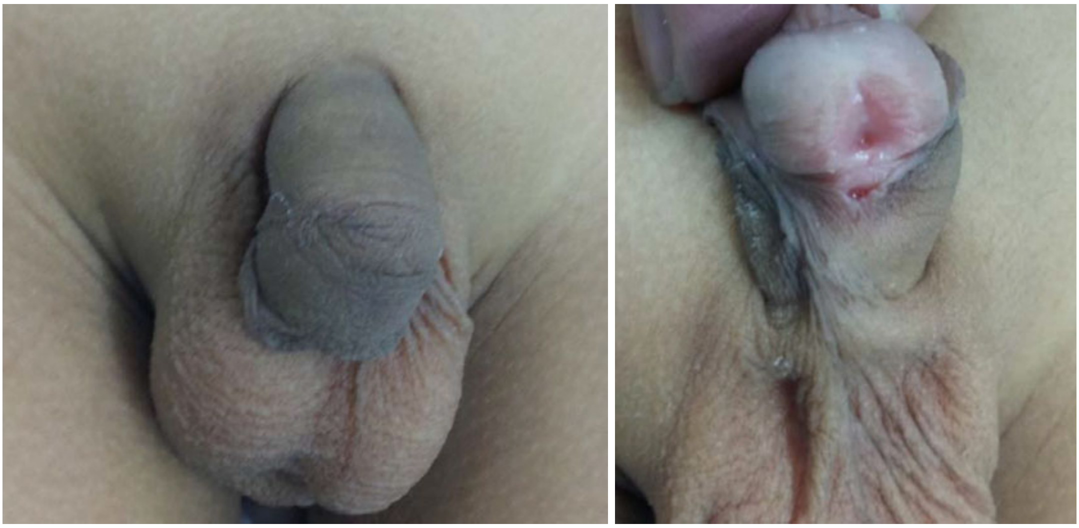
- Open surgical circumcision (Figs. 22.4 and 22.5):
  - This is usually performed under general anesthesia
  - Open surgical circumcision is performed for adults, older children or for those with associated anomalies of the penis such as webbed penis, chordee and deviation of the penis.
  - The amount of foreskin to be removed is determined and excised
  - The edges of the skin are sutured with absorbable sutures.
  - The end result is a cosmetically acceptable penis.
- For infant circumcision, devices such as the Gomco clamp, Plastibel and Mogen clamp are commonly used.
- These follow the same basic procedure.
  - First, the amount of foreskin to be removed is estimated. The practitioner opens the foreskin via the preputial orifice to reveal the glans underneath and ensures it is normal before bluntly separating the inner lining of the foreskin (preputial epithelium) from its attachment to the glans.
  - The practitioner then places the circumcision device (this sometimes requires a dorsal slit).
  - Finally, the foreskin is excised.
- The AAP Task Force on Circumcision recommends the use of environmental, nonpharmacological, and pharmacologic interventions to reduce pain and distress during neonatal circumcision. These interventions include:
  - The use of a sucrose pacifier
  - The use of paracetamol suppositories
  - The use of EMLA cream (a mixture of prilocaine and lidocaine)
  - The use of penile nerve blocks (e.g. 0.5 % lidocaine without epinephrine)
    - A ring block that consists of the circumferential subcutaneous injection of local anesthesia
    - A dorsal penile block
  - Oral acetaminophen or paracetamol suppositories provides adequate pain control after neonatal circumcision.
  - In patients who undergo formal surgical circumcisions in the operating room, caudal blocks and dorsal penile blocks decrease the amount of pain medication required after the procedure.


Figs. 22.4 and 22.5 Clinical photographs showing open surgical circumcision

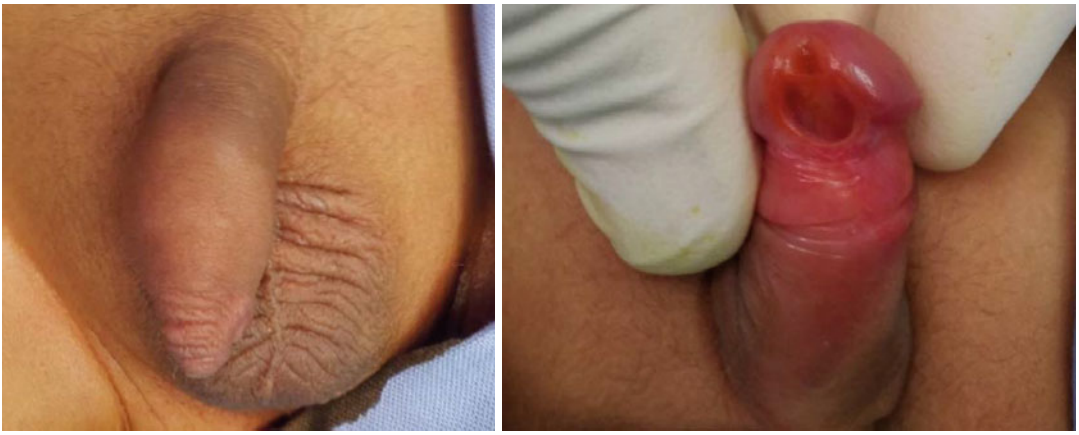
- The use of unipolar diathermy during circumcision should be avoided.
- Prior to circumcision, it is important to determine the presence of a normal glans and penis without any evidence of hypospadias, epispadias, chordee, or other anomalies.
- Most cases of hypospadias or epispadias are evident clinically and these should not be circumcised.
- The foreskin in these patients can be used during the repair of hypospadias or epispadias.
- Circumcision is part of the repair of these patients.
- Epispadias is characterized by a deficient foreskin and a dorsally placed urethral opening (Figs. 22.6 and 22.7).
- Hypospadias is characterized by a deficient foreskin ventrally while the dorsally the foreskin is well formed like a hood. The urethral opening is placed ventrally (Figs. 22.8 and 22.9).
- A point of caution is in patients with mega meatus variant of hypospadias. These patients have a normal well developed and complete foreskin.
- This variant is called, the mega meatus intact prepuce (MIP) variant.
- The urethral meatus in these patients is large (mega meatus) (Figs. 22.10 and 22.11).
- These patients have a well-developed foreskin and the diagnosis of mega meatus is only made at the time of circumcision.



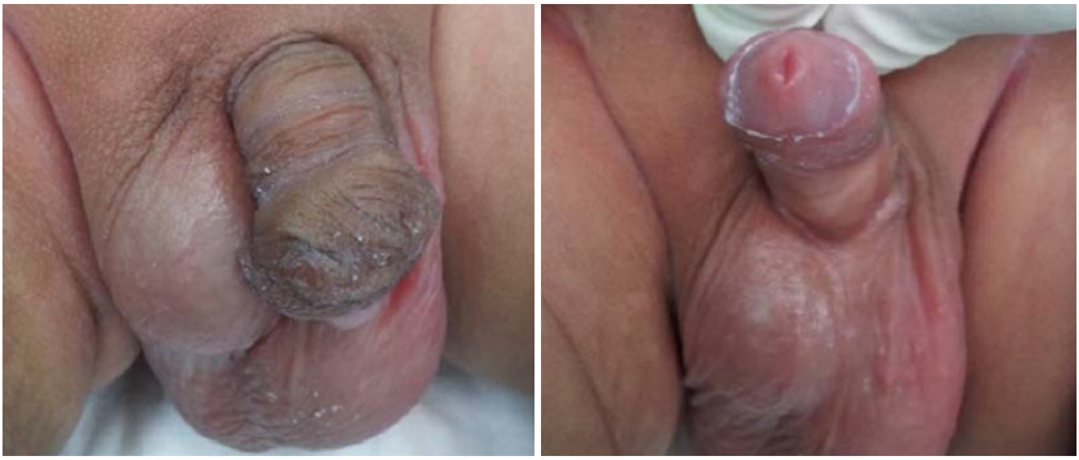
Figs. 22.6 and 22.7 Clinical photographs showing epispadias. Note the dorsally located urethral opening



Figs. 22.8 and 22.9 Clinical photographs showing hypospadias. Note the deficient foreskin ventrally and the hood like foreskin dorsally. Note also the abnormally located urethral opening on the ventral aspect of the penis



Figs. 22.10 and 22.11 Clinical photographs showing an infant with a megameatus. Note the normal looking foreskin. Note also the abnormally large meatus



Figs. 22.12 and 22.13 Clinical photographs showing an infant with a foresking resembelling that of hypospadias but a normally located urethral meatus

- Once the diagnosis is confirmed, circumcision is abandoned and postponed to be done at the time of repair of Mega meatus.
- Rarely, a deficient prepuce ventrally but a normally situated meatus is seen (Figs. 22.12 and 22.13).
- The surgical procedure of male circumcision may involve one of various devices including:
  - The Circumplast
  - The Gomco clamp
  - The Plastibell
  - The Mogen clamp
  - The Shang ring
  - The bone cutter
- The bone cutter is rarely used nowadays (Fig. 22.14).
- Plastibel Circumcision (Figs. 22.15, 22.16, 22.17, 22.18, 22.19, 22.20, 22.21, 22.22, 22.23, 22.24, 22.25, 22.26, 22.27, and 22.28):
  - First, the amount of foreskin to be removed is estimated.
  - The preputial orifice is widened with an artery forceps and the foreskin is opened.
  - This will reveal the glans underneath and ensure it is normal.
  - The inner lining of the foreskin (preputial epithelium) is bluntly separated from its attachment to the glans.

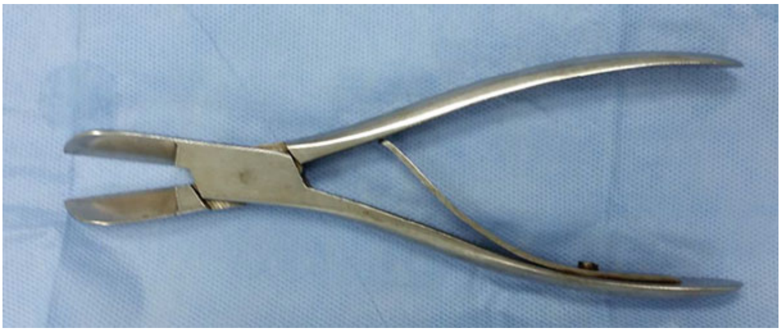


Fig. 22.14 A photograph showing a bone cutter that is used for circumcision

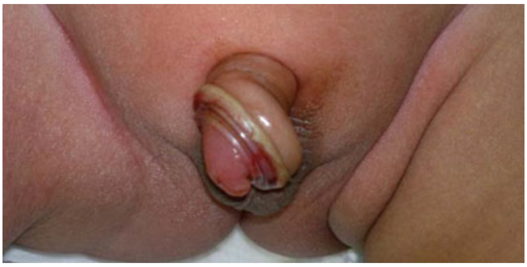


Fig. 22.15 A clinical photograph showing plastibel circumcision. The size of the plastibel is large for the size of the penis

- The area is cleaned and any smegma is removed.
- The size of the plastibel to be used is estimated based on the size of the glans penis. Improper plastibel size will give unsatisfactory results (Fig. 22.15).
- Plastibel come in different sizes: 1.1, 1.2, 1.3, 1.4, 1.5 and 1.7.
- A dorsal slit is made in the prepuce. This will help and facilitate introducing the plastibel.
- To minimize bleeding from the dorsal slit edges, each edge is held with an artery forceps.
- The plastibel is placed over the glans and the edges of the dorsal slit are pulled by an assistant who also pushes the plastibel and keep it in place.
- A ligature is applied around the foreskin and firmly tied in an already made groove in the plastibel. The pushed plastibel protect the glans penis.
- Finally, the foreskin distal to the plastibel is amputated.
- The handle of the plastibel is snapped of the plastibel.
- Sometimes, the frenulum band may need to be broken or crushed and cut from the corona near the urethra to ensure that the glans can be freely and completely exposed. This may nictitates the use of diathermy to control bleeding. Only bipolar diathermy is used and monopolar diathermy should be avoid. There are small battery operated portable bipolar diathermy which can be used for this purpose (Figs. 22.29, 22.30, 22.31, and 22.32).
- The tied suture causes ischemic necrosis of the remaining foreskin which falls down together with the plastibel in 5–7 days (Figs. 22.33, 22.34, 22.35, and 22.36).
- A plastibel that does not fall after 7 days should be removed.

- There are also restrainers which can be used during plastibel circumcision to control the movement of the infant (Fig. 22.37).
- Circumplast circumcision (Fig. 22.38):
  - The procedure is similar to the plastibel
  - The glans is freed
  - The Circumplast is placed over the glans, and the foreskin is placed over the Circumplast.
  - A ligature is then tied firmly around the foreskin and tightened into a groove in the Circumplast to achieve hemostasis.
  - The foreskin distal to the ligature is excised and the handle is snapped off the Circumplast device.
  - The Circumplast falls from the penis after the wound has healed, typically in 4–6 days.

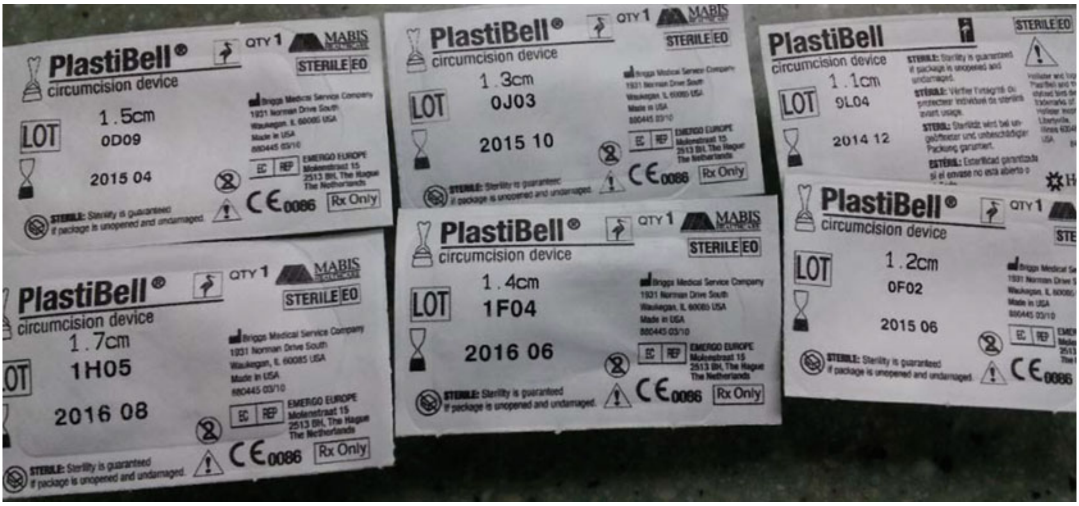
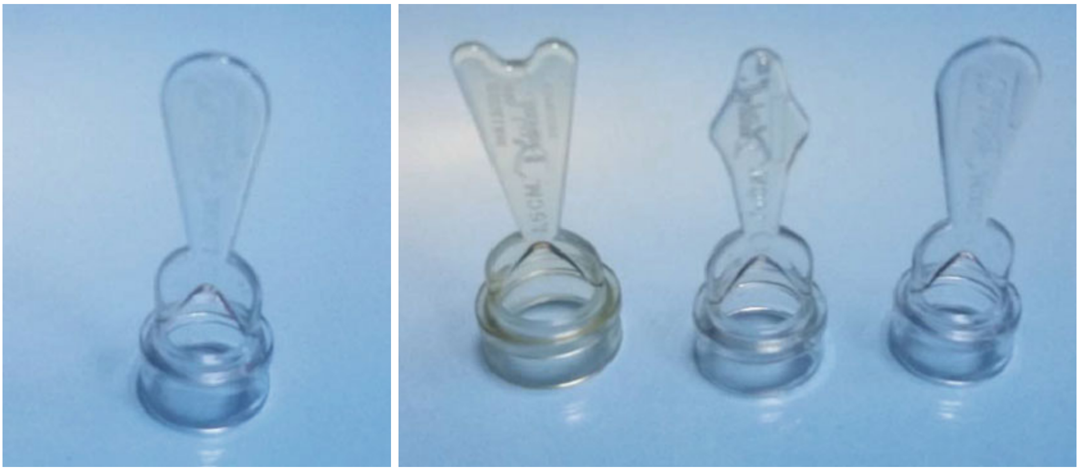
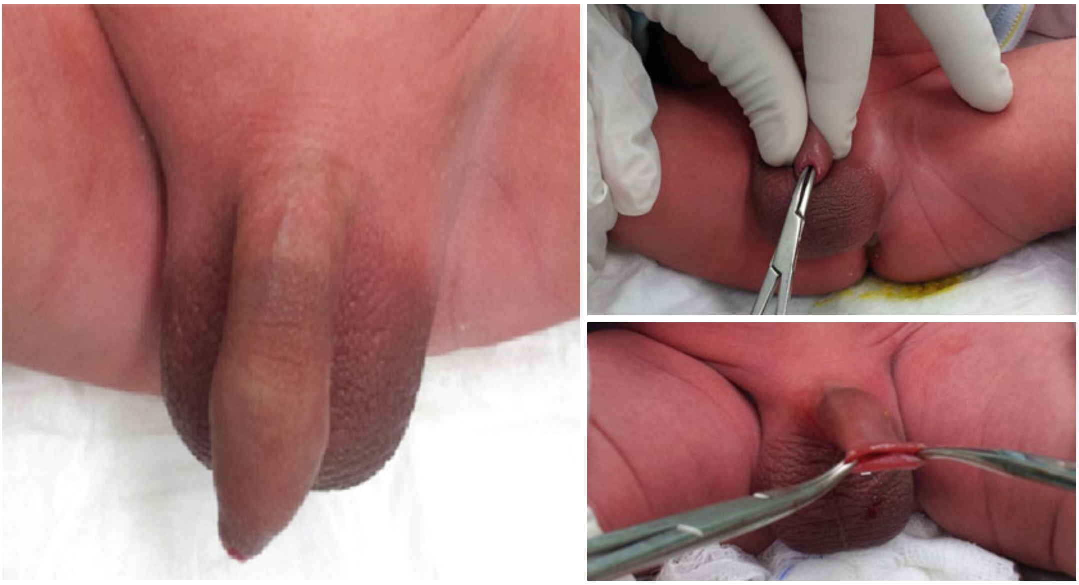

PlastiBell® circumcision device
1.5cm
0D09
2015 04
1.3cm
0J03
2015 10
1.1cm
9L04
2014 12
1.7cm
1H05
2016 08
1.4cm
1F04
2016 06
1.2cm
0F02
2015 06
LOT
STERILE EO
Rx Only
MABIS

Fig. 22.16 A photograph showing the different sizes of plastibells

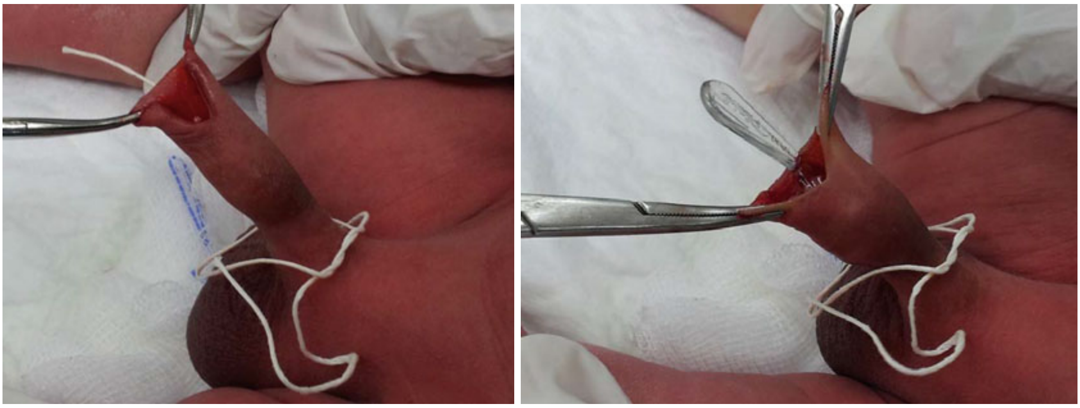


Figs. 22.17 and 22.18 Photographs showing the different shapes of plastibells

- Gomco clamp circumcision (Fig. 22.39):
  - The foreskin is dorsally crushed with a hemostat and then slit with scissors from the tip to the coronal sulcus.
  - The foreskin is drawn over the bell shaped portion of the clamp and inserted through a hole in the base of the clamp.
  - The clamp is tightened, "crushing the foreskin between the bell and the base plate."
  - The crushed blood vessels provide hemostasis. The flared bottom of the bell fits tightly against the hole of the base plate, so the foreskin may be cut away with a scalpel from above the base plate.
- Mogen clamp circumcision (Figs. 22.40, 22.41, 22.42, and 22.43):
  - The foreskin is pulled dorsally with a straight hemostat, and lifted.
  - The Mogen clamp is then slid between the glans and hemostat, following the angle of the corona to "avoid removing excess skin ventrally and to obtain a superior cosmetic result" to Gomco or Plastibell circumcisions.
  - The clamp is locked, and a scalpel is used to cut the skin from the flat (upper) side of the clamp.

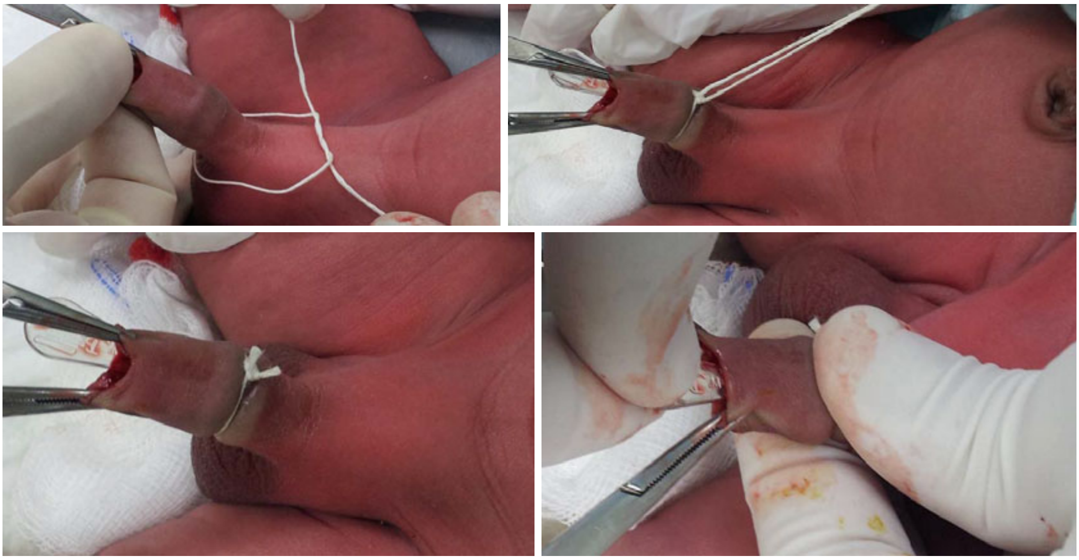


Figs. 22.19, 22.20, and 22.21 Clinical photographs showing an uncircumcised infant. The preputial opening is dilated and opened



Figs. 22.22 and 22.23 Clinical photographs showing the dorsal slit and the introduced plastibell. The suture for tining is already prepared

- The Shang ring circumcision (Figs. 22.44 and 22.45):
  - The Shang Ring is a disposable MC device invented by Mr. Jianzhong Shang in China.
  - It is commercially available in China in 32 sizes, ranging from 9 to 42 mm in diameter, for use with neonates to adults.
  - The Shang Ring consists of two parts, an inner ring and an outer ring.
  - The inner ring has a shallow groove on its outer surface that is lined by a silicone band which confers a non-bioreactive surface against which the outer ring sandwiches the foreskin.
  - The outer ring consists of two halves that are hinged together at one end.
  - The outer ring is closed securely via a ratchet style closure.
  - Hemostasis provided by the locking rings minimizes bleeding and removes the need for sutures.



Figs. 22.24, 22.25, 22.26, and 22.27 Clinical photographs showing the ligature being tied. Following this the handle of the plastibell is broken

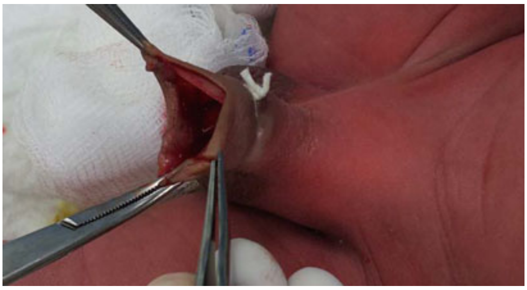
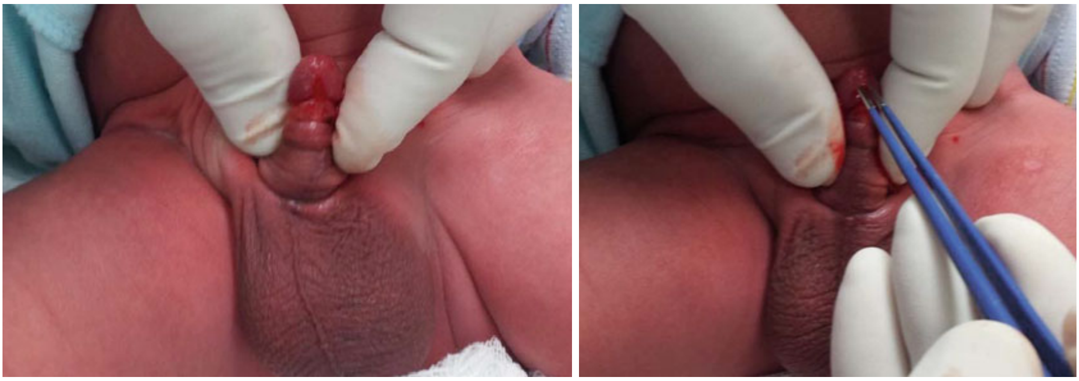


Fig. 22.28 A clinical photograph showing the foreskin being cut

22.8 Complications of Circumcision

- Neonatal circumcision is generally safe when done by an experienced practitioner.
- The most common acute complications are bleeding, infection and the removal of either too much or too little foreskin.
- These complications occur in approximately 0.12 % of procedures.
- Minor complications are reported to occur in 3 % of procedures.
- Complication rates are greater when the procedure is performed by an inexperienced operator, in unsterile conditions, or when the child is at an older age.
- Significant acute complications happen rarely, occurring in about 1 in 500 newborn procedures.
- Severe to catastrophic complications are sufficiently rare that they are reported only as individual case reports.
- Other possible complications include buried penis, chordee, phimosis, skin bridges, urethral fistulas, and meatal stenosis.
- These complications may be avoided with proper technique.
- The circumcision procedure may carry the risks of heightened pain response for newborns and dissatisfaction with the result.
- Newborns that experience pain due to being circumcised have different responses to vaccines given afterwards, with higher pain scores observed.
- There are several complications known to be associated with neonatal circumcision.
- These complications include:
  - Bleeding is the most common early complication (Fig. 22.46)
    - This is commonly from the frenulum blood vessels but can be also from the cut edges of the foreskin or the dorsal vessels.
    - This is usually controlled with local hemostatic measures, such as pressure dressings.

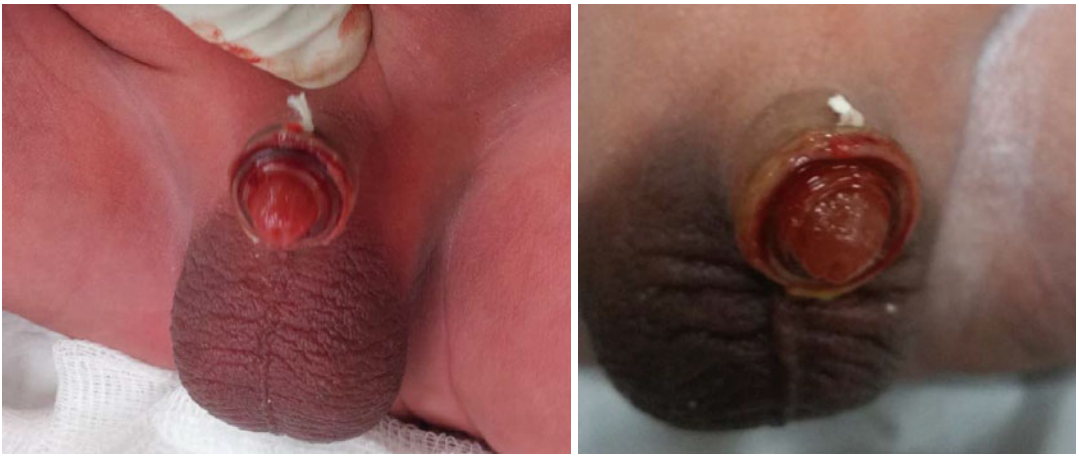


Figs. 22.29 and 22.30 Clinical photographs showing the site of the frenulum where most bleeding occurs. These vessels can be cauterized using pipolar diathermy

Figs. 22.31 and 22.32 Photographs showing small portable cautery which can be used to control bleeding at the time of circumcision

    - Surgicele or other hemostatic agents can be applied also. A small piece of surgicele can be inserted in the grove between the glans penis and the plastibel to control bleeding.
    - If these measures fail, the patient must be taken to the operating room for surgical hemostasis and hematoma evacuation.
  - Infection is the second most common early postoperative complication, but usually is minor and easily managed with oral and topical antibiotics.
  - The most common long-term complication seen after circumcision is meatal stenosis (Figs. 22.47 and 22.48).

- Other complications described include the followings:
  - Recurrent phimosis
  - Wound separation
  - Penile torsion
  - Concealed penis (Figs. 22.49 and 22.50)
  - Unsatisfactory cosmetic appearance (Figs. 22.51, 22.52, 22.53, and 22.54)
  - Skin bridges (Figs. 22.55, 22.56, and 22.57)
  - Urinary retention
  - Meatitis
  - Skin chordee (due to removal of excessive skin) (Fig. 22.58)
  - Inclusion cysts
  - Retained Plastibel devices (Fig. 22.59)
  - Incomplete circumcision (Fig. 22.60)
  - Scalded skin syndrome
  - Necrotizing fasciitis
  - Sepsis
  - Meningitis
  - Urethral fistula
  - Penile necrosis
  - Amputation of a portion of the glans penis
  - Gangrene of the glans penis (Fig. 22.61)
  - Urethral fistula (Fig. 22.62)
- Sexual effects:
  - Circumcision does not appear to decrease the sensitivity of the penis, harm sexual function or reduce sexual satisfaction.
  - A 2013 systematic review found that circumcision did not appear to adversely affect sexual desire, pain with intercourse,



Figs. 22.33 and 22.34 Clinical photographs showing the final stage of plastibel circumcision. The use of proper size of plastibel is important

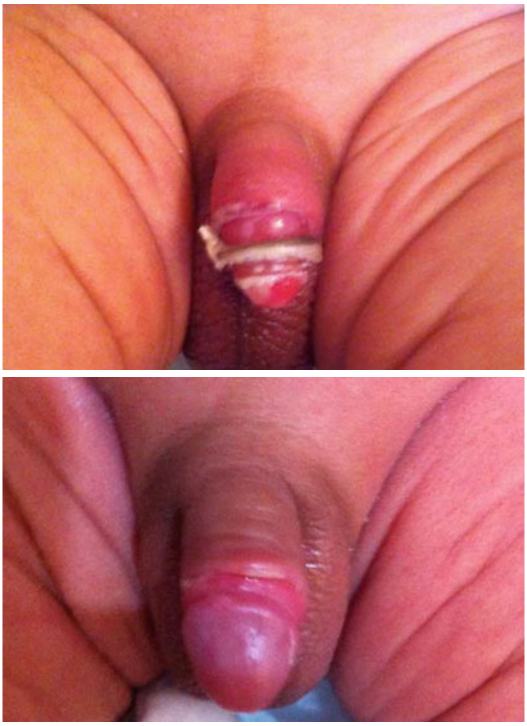


Fig. 22.35 and 22.36 Clinical photographs showing the plastibel circumcision. Note the plastibel falling down

  premature ejaculation, time until ejaculation, erectile dysfunction or difficulties with orgasm.
  - Another 2013 systematic review reported no adverse effects of circumcision on sexual function, sensitivity, sensation or satisfaction.

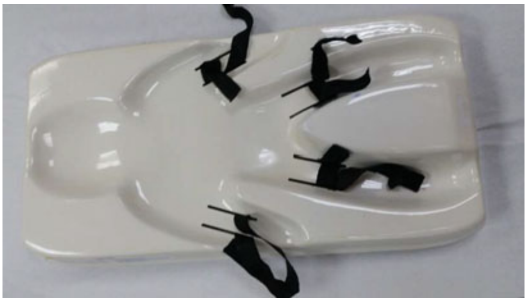


Fig. 22.37 A photograph of a restrainer that can be used during plastibel circumcision

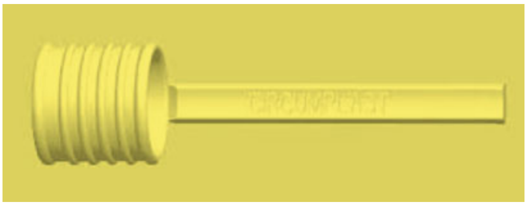


Fig. 22.38 A photograph showing circumplast

- Psychological effects:
  - Behavioral effects have been observed following circumcision including changes in sleep patterns, irritability, changes in feeding, and parental bonding.
  - Some men who were involuntarily circumcised described their feelings about the procedure using the terms “violation, torture, mutilation and sexual assault”.

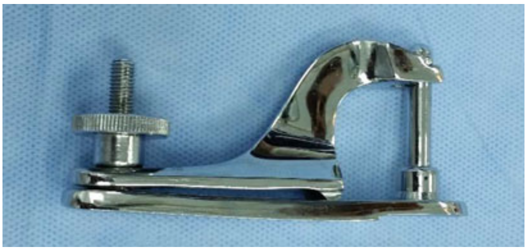
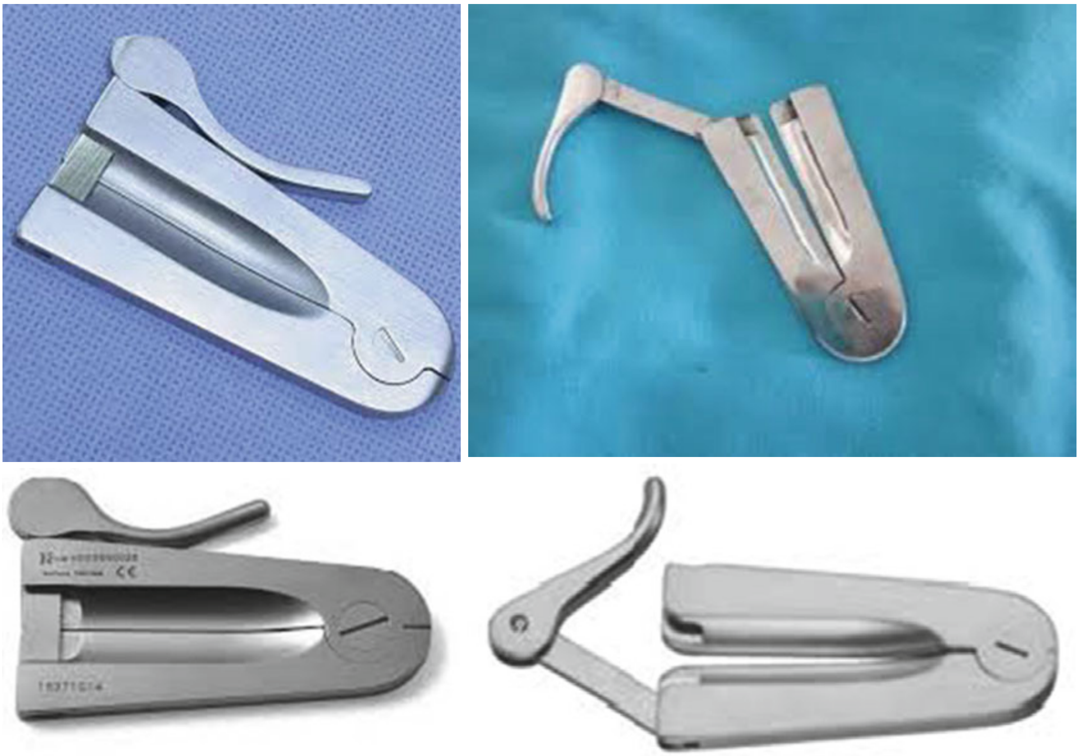
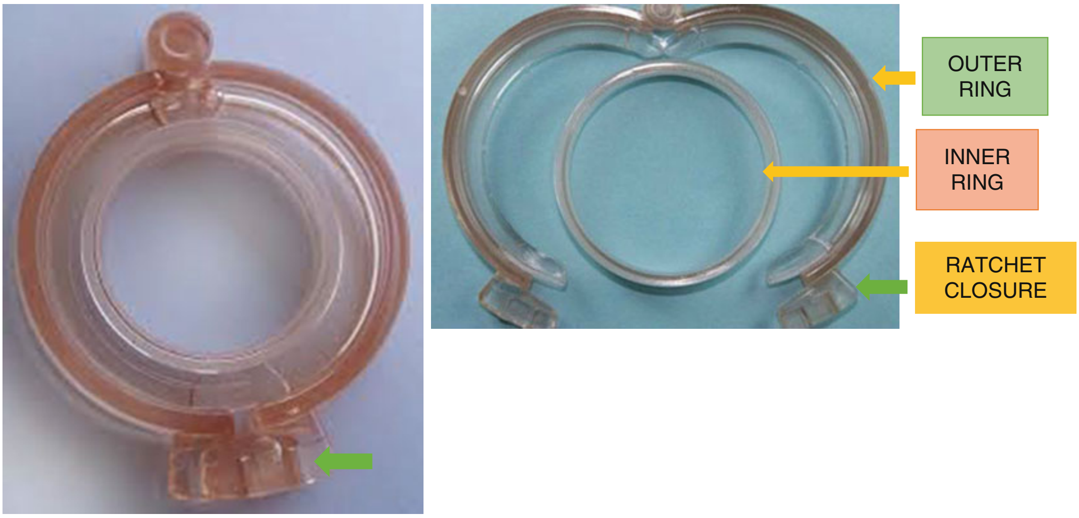


Fig. 22.39 A photograph showing the Gomco device



Figs. 22.40, 22.41, 22.42, and 22.43 Photographs showing the Mogen clamp


OUTER RING
INNER RING
RATCHET CLOSURE

Figs. 22.44 and 22.45 Photographs showing the Shang ring

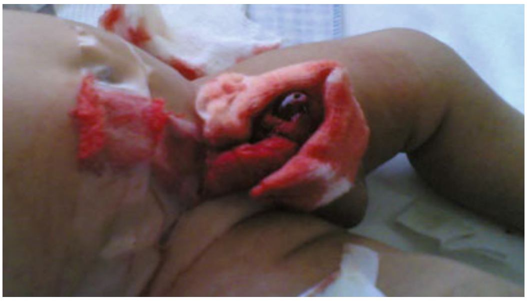
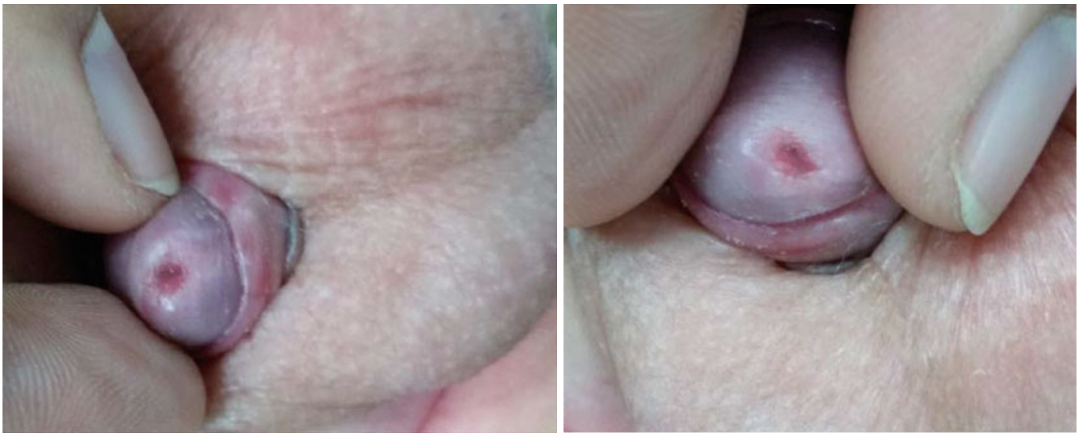
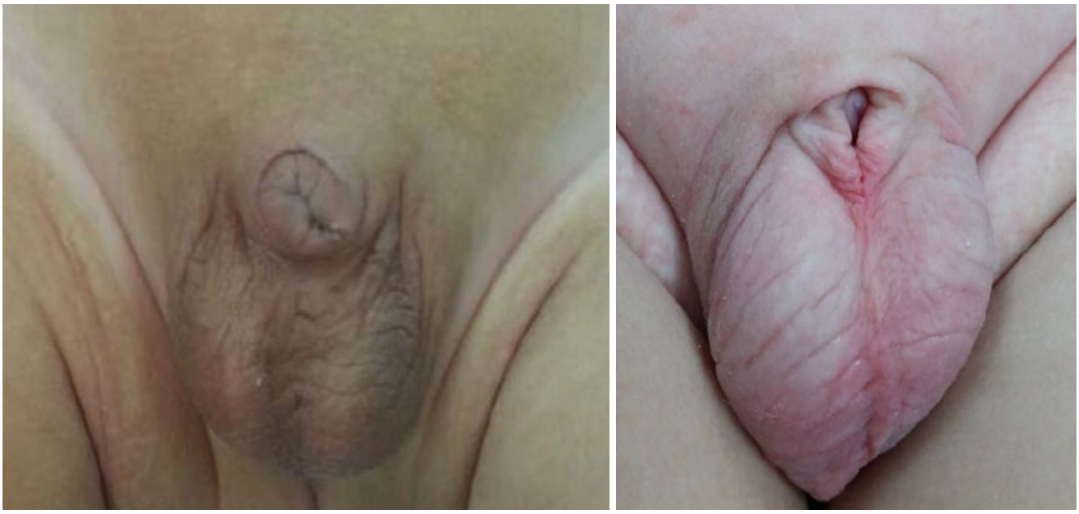


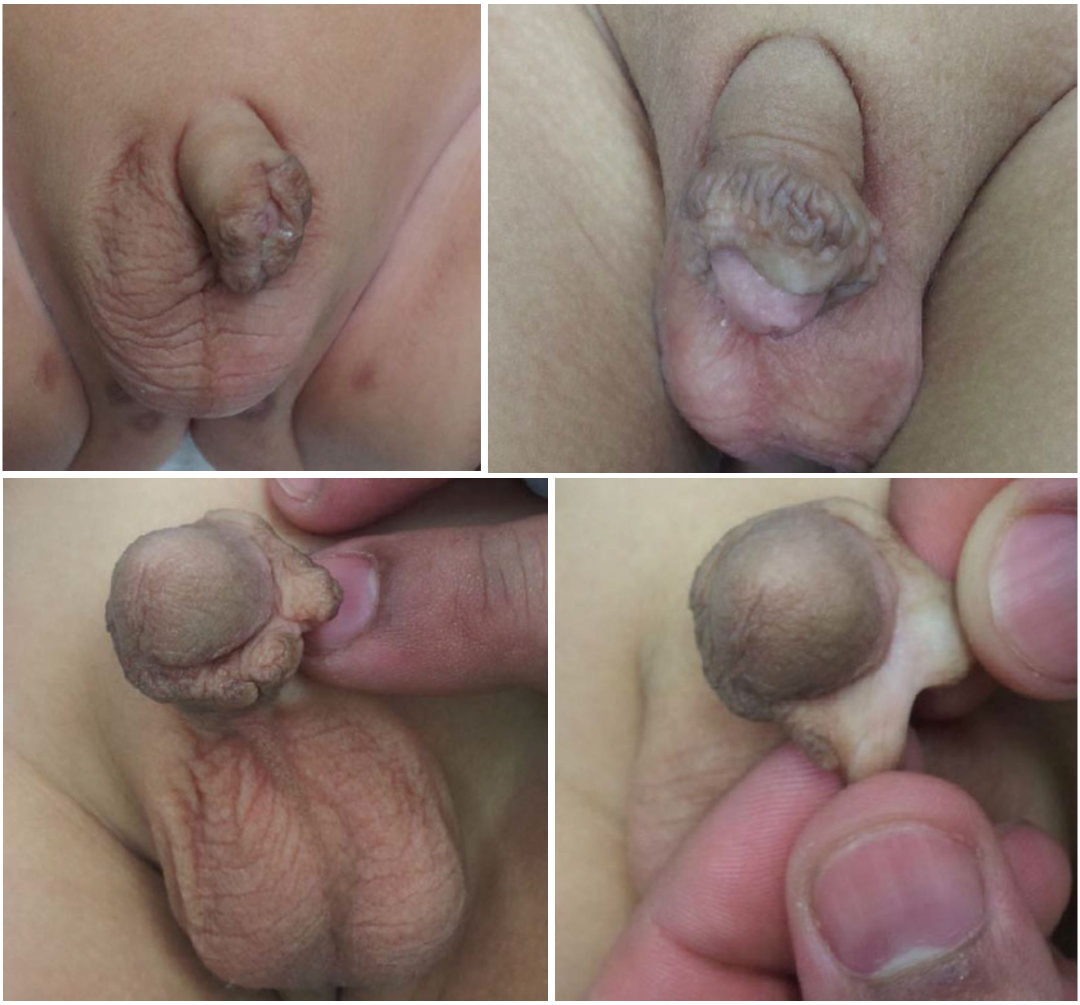
Fig. 22.46 A clinical photograph showing bleeding following circumcision



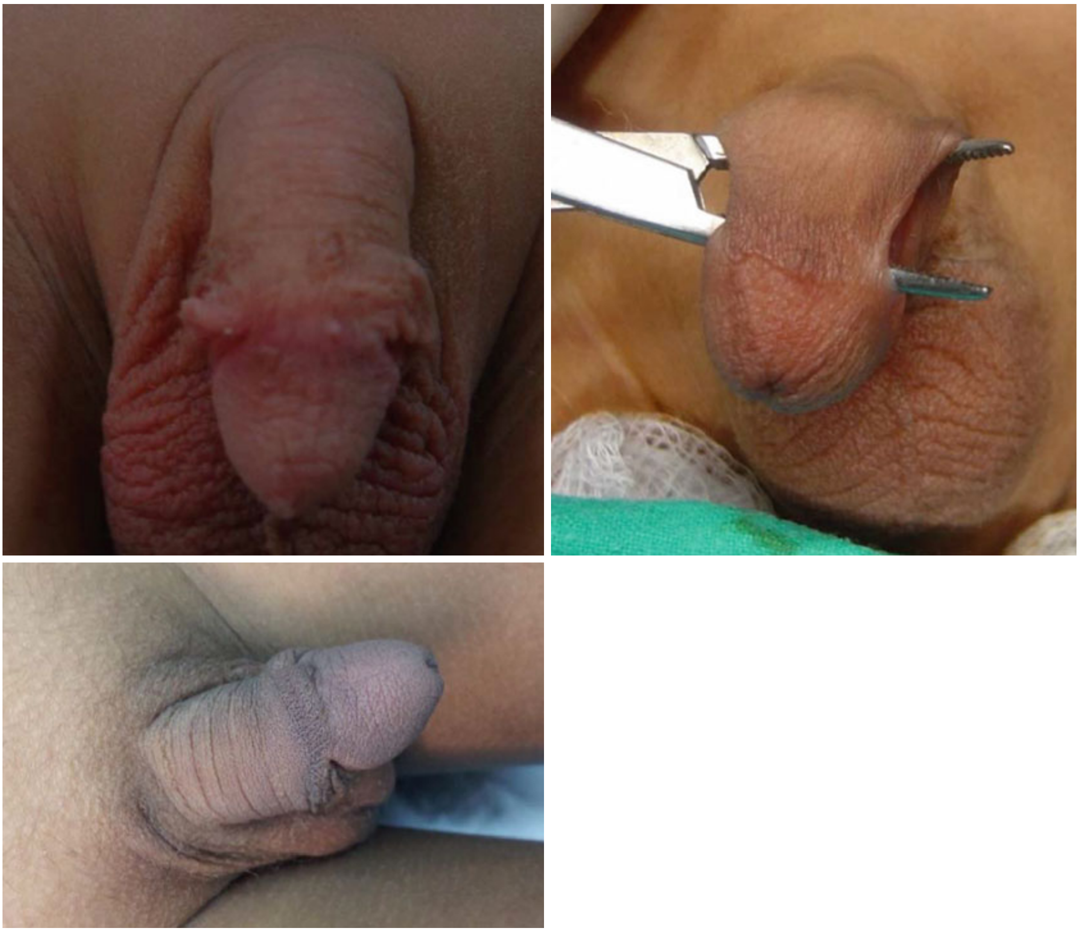
Figs. 22.47 and 22.48 Clinical photographs showing meatal stenosis



Figs. 22.49 and 22.50 Clinical photographs showing concealed penis following circumcision



Figs. 22.51, 22.52, 22.53, and 22.54 Clinical photographs showing unsatisfactory cosmesis following circumcision



Figs. 22.55, 22.56, and 22.57 Clinical photographs showing skin bridges following circumcision

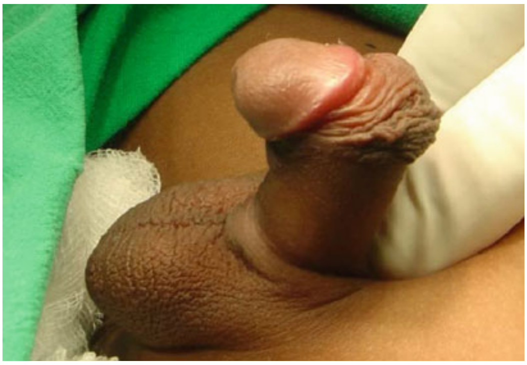


Fig. 22.58 A clinical photograph showing chordee

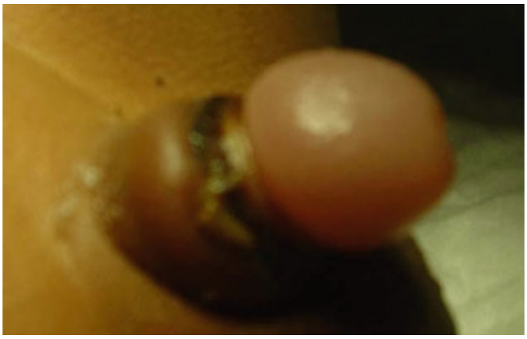


Fig. 22.59 A clinical photograph showing a retained plastibel. Note the associated swelling of the glans penis

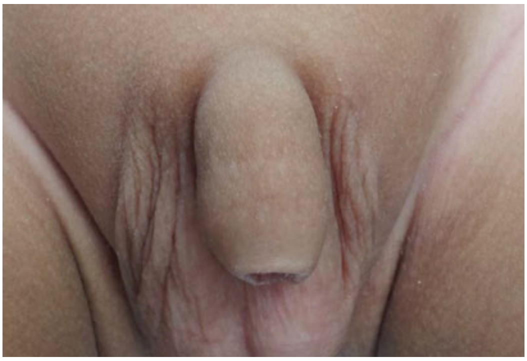


Fig. 22.60 A clinical photograph showing incomplete circumcision

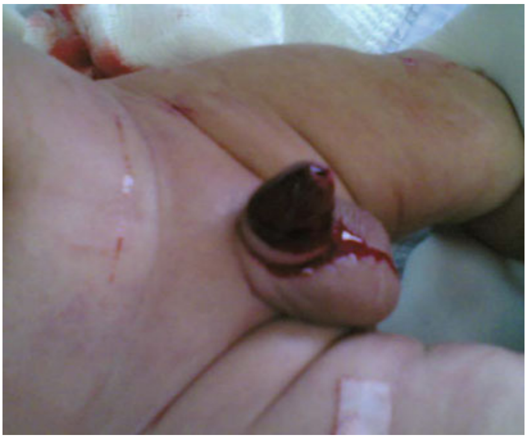


Fig. 22.61 A clinical photograph showing gangrenous glans penis following circumcision

Further Reading

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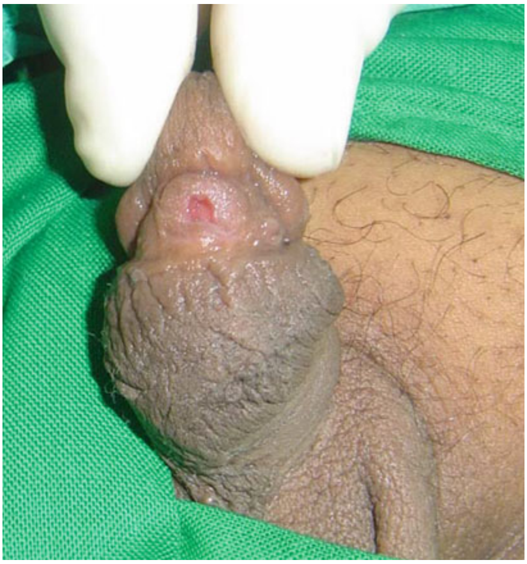

Fig. 22.62 A clinical photograph showing a urethral fistula following circumcision

Priapism in Children

23

23.1 Introduction

- Priapism is defined as a prolonged, non-physiologic, sustained and painful erection.
  - It is not provoked by sexual stimulation or arousal
  - It persists after ejaculation and orgasm.
- Priapism is an uncommon condition that needs to be recognized early and immediate medical attention is important.
- It is considered a true medical and urologic emergency, and early intervention allows the best chance for functional recovery.
- Prompt diagnosis and treatment of priapism are important to prevent tissue damage that could result in the inability to get or maintain an erection (erectile dysfunction).
- Such a prolonged erection causes physiological changes by 6 h, cellular damage by 24 h, and fibrosis by 36 h, resulting in permanent erectile dysfunction.
- Priapism can present in childhood and adolescence.
- It is most commonly seen between ages 5 and 10 in boys and ages 20 and 50 in men.
- Nocturnal episodes of priapism are more frequent.
- Priapism is frequently idiopathic in etiology but it is a known complication of a number of important medical conditions and pharmacologic agents.
- More than one-fourth of priapism episodes are caused by sickle cell disease (SCD).
- At least one-third of male adults with SCD present with priapism at some point, usually beginning in school age.
- Nearly one-fourth of priapism in patients with SCD present during the prepubertal period.
- The mean age for the onset of priapism in patients with SCD is 11 years.
- In patients with SCD, priapism rarely present for the first time after the third decade of life.
- In children nearly all cases of priapism are secondary to sickle cell disease or trauma.
- Priapism in childhood commonly presents as a complication of sickle cell disease (SCD) (Figs. 23.1 and 23.2).
- The frequency of priapism in children with SCD varies between 2 and 6 %.
- Priapism normally involves the two corpora cavernosa and spares the corpora spongiosum.
- Priapism as a complication of SCD can cause persistent impotence, erectile dysfunction and behavioral sexual problems (Figs. 23.3).
- A prior history of priapism makes these patients fear any sexual activities as these may induce an episode of priapism.
- In patients with SCD:
  - Priapism was first reported in SCD patients in 1934.
  - The most frequent form of priapism in patients with SCD is recurrent self-limited short episodes (stuttering priapism)
  - Acute episodes of priapism are defined as painful erection and/or persisting more than 4–6 h.

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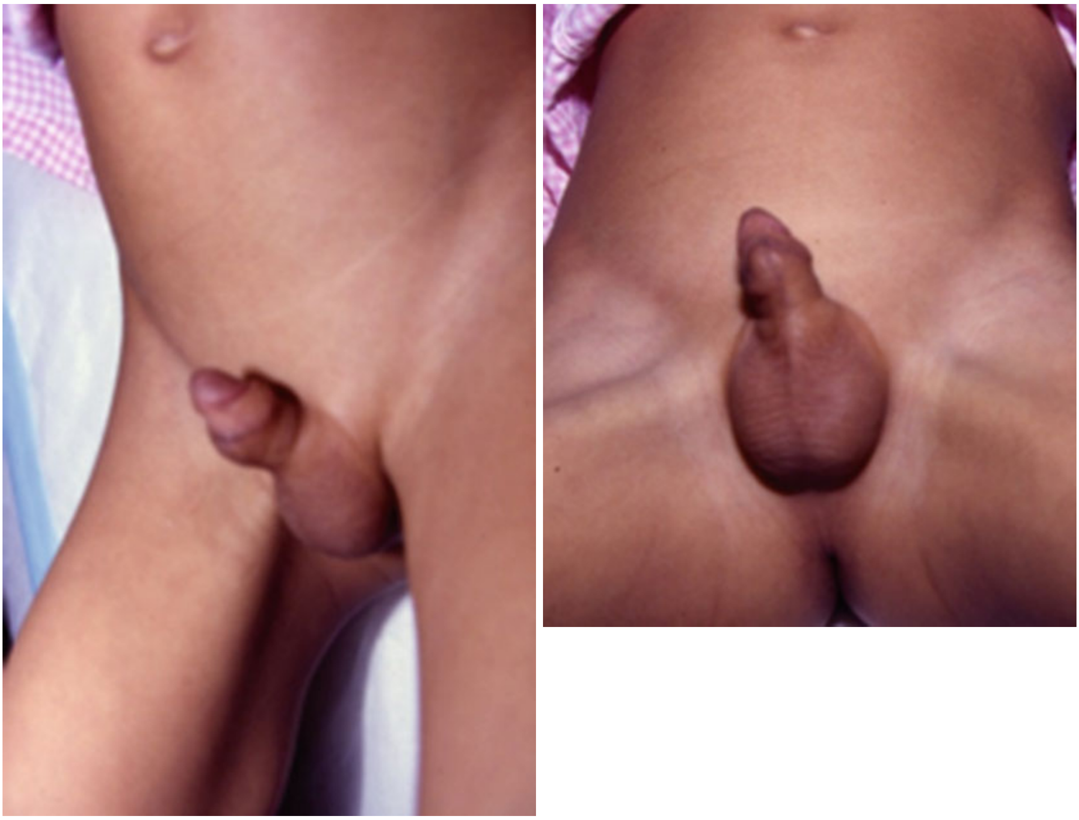
A.H. Al-Salem, *An Illustrated Guide to Pediatric Urology*, DOI 10.1007/978-3-319-44182-5_23



Figs. 23.1 and 23.2 Clinical photographs showing priapism in a child

  - Approximately two-third of patients presenting with an acute attack of priapism report previous intermittent episodes.
- Priapism is classified into high or low blood flow.
- It is important to differentiate between the two types as this important in terms of treatment and prognosis.
- High flow priapism (Nonischemic priapism) is characterized by an increase of arterial supply to the corpora cavernosa while the venous drainage remains normal.
- Low flow priapism (Ischemic priapism) is characterized by loss of vascular regulation and the venous drainage is impaired, presumably as a consequence of vascular blockage by deformed red blood cells.
- It is estimated that more than 80 % of patients with SCD have low flow priapism and occasionally it may be high flow priapism.
- Low-flow priapism is by far the most common type.
- High-flow priapism is rare and is usually a result of blunt trauma to the corpora cavernosus resulting in arteriovenous fistula.
- The treatment for high-flow priapism is surgical identification and obliteration of fistulas.
- Causes of low-flow priapism include the followings:
  - Idiopathic
  - Hematologic (e.g. sickle cell, leukemia)
  - Pharmacologic adverse effects (e.g. psychiatric medications)
  - Therapeutic medications (e.g. oral erectile medications, intracavernous injections)
  - Neoplastic
  - Others (e.g. surgical, traumatic, neurogenic, infectious)

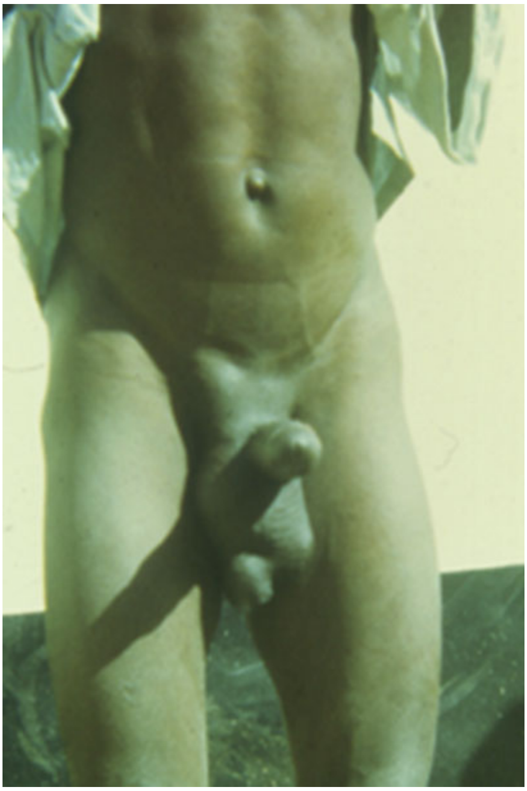


Fig. 23.3 Clinical photograph of an adult with priapism

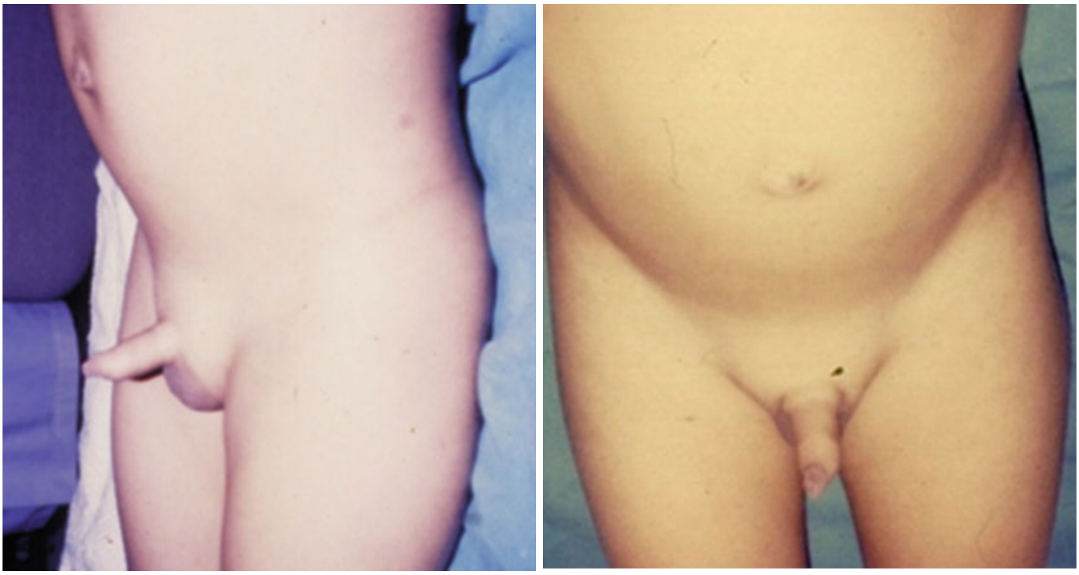
- Management of low flow priapism should achieve resolution as promptly as possible.
- Early intervention allows the best chance for functional recovery and minimize the sequelae.
- Treatment of low-flow priapism should progress in a stepwise fashion, starting with therapeutic aspiration, with or without irrigation of the corpora. If this fails, intracavernous injection of sympathomimetic drugs is the next step.
- Rapid resolution of ischaemic (low flow) priapism prevents permanent cavernosal structural damage and is associated with improved prognosis for potency later in life.

23.2 Pathophysiology

- The penis is made up of three corporeal erectile tissues, two corpora cavernosa on the dorsum of the penis and corpora spongiosum ventrally.
- The urethra runs within the corpora spongiosum.
- The erectile tissue within the corpora contains arteries, nerves, muscle fibers, and venous sinuses lined with flat endothelial cells, and it fills the space of the corpora cavernosa.
- The cut surface of the corpora cavernosa looks like a sponge. There is a thin layer of areolar tissue that separates this tissue from the tunica albuginea.
- Blood flow to the corpora cavernosa is via the paired deep arteries of the penis (cavernosal arteries), which run near the center of each corpora cavernosa.
- Normally, erection occurs in response to physical or psychological stimulation.
- Erection is the result of smooth-muscle relaxation and increased arterial flow into the corpora cavernosa, causing engorgement and rigidity.
- Corporeal relaxation causes external pressure on the emissary veins exiting the tunica albuginea, trapping blood in the penis and causing erection.
- Engorgement of the corpora cavernosa compresses the venous outflow tracts (i.e. subtunical venules), trapping blood within the corpora cavernosa.
- Erection is induced by the parasympathetic autonomic nervous system.
- This stimulation causes penile blood vessels to relax and expand, increasing blood flow to the spongy tissues in the penis.
- The major neurotransmitter that controls erection is nitric oxide, which is secreted by the endothelium that lines the corpora cavernosa. These events occur in both normal and pathologic erections.
- Sexual stimulation causes the release of nitric oxide (NO) via stimulation of noradrenergic norcholinergic neurons, provoking a local increase of cyclic GMP (cGMP) by the activation of guanylate-cyclase.
- NO-activated intracellular guanylate cyclase, converting guanosine triphosphate (GTP) to cyclic guanosine monophosphate (cGMP), causes relaxation of cavernosal arteries and

increased penile blood flow, resulting in erection.

- Cyclic GMP then enhances the cellular efflux of calcium and the relaxation of smooth muscle of efferent arteries and of the corpora cavernosa itself. This will lead to an increase in the afferent blood flow.
- The draining venules which are located between the corpora cavernosa, are passively compressed by the rigid congested corpora and as a result blood accumulates.
- Consequently, the blood-filled penis becomes erect.
- The erection process ends by ejaculation and orgasm.
- As a result of this, signals are sent to the sympathetic nervous system which determines the vasoconstriction of the efferent arteries of the corpora cavernosa, leading to reduction in the blood inflow.
- This will lead to an increase in venous drainage mechanisms and detumescence results. The blood flows out of the penile blood vessels, and the penis returns to its nonrigid (flaccid) state.
- Pathophysiologically, priapism can be of either a low-flow (ischemic) or a high-flow (nonischemic) type.
- Low-flow priapism, which is by far the most common type, results from failure of venous outflow, whereas high-flow priapism results from uncontrolled arterial inflow.
- Clinically, differentiation of low-flow from high-flow priapism is critical, because treatment and prognosis for each is different.
- Low-flow priapism may be due to any of the following:
  - An excessive release of neurotransmitters
  - Blockage of draining venules (e.g., mechanical interference in sickle cell crisis, leukemia, or excessive use of intravenous parenteral lipids)
  - Paralysis of the intrinsic detumescence mechanism
  - Prolonged relaxation of the intracavernous smooth muscles (most often caused by the use of exogenous smooth-muscle relaxants such as injectable intracavernosal prostaglandin E1)
- Prolonged low-flow priapism leads to a painful ischemic state, which can cause fibrosis of the corporeal smooth muscle and cavernosal artery thrombosis. The degree of ischemia is a function of the number of emissary veins involved and the duration of occlusion.
- Light-microscopy studies conducted early demonstrated that corporeal tissue becomes thickened, edematous, and fibrotic after days of priapism.
- Further studies with electron microscopy have demonstrated trabecular interstitial edema after 12 h of priapism and destruction of sinusoidal endothelium, exposure of the basement membrane, and thrombocyte adherence after 24 h of priapism. At 48 h, thrombi were evident in the sinusoidal spaces and smooth-muscle cell.
- Histopathologic findings varied from necrosis to fibroblast-like cell transformation. Priapism for longer than 24 h is associated with permanent impotence.
- High-flow priapism is the result of uncontrolled arterial inflow from a fistula between the cavernosal artery and the corpus cavernosum. This is generally secondary to blunt or penetrating injury to the penis or perineum causing rupture of a cavernous artery. It is usually not painful.
- In priapism, the corpus spongiosum and glans penis are typically not engorged.
- Ischemic (low flow) priapism can cause serious complications.
  - The blood trapped in the penis is deprived of oxygen.
  - When an erection lasts for longer than 4 h, this oxygen-poor blood can begin to damage or destroy tissues in the penis.
- As a result, untreated priapism may cause:
  - Erectile dysfunction, the inability of the penis to become or stay erect with sexual arousal
  - Disfigurement of the penis
- Sickle cell anemia is the most common cause of priapism in boys (Figs. 23.4 and 23.5).
- Priapism can be primary or idiopathic and secondary to other factors.

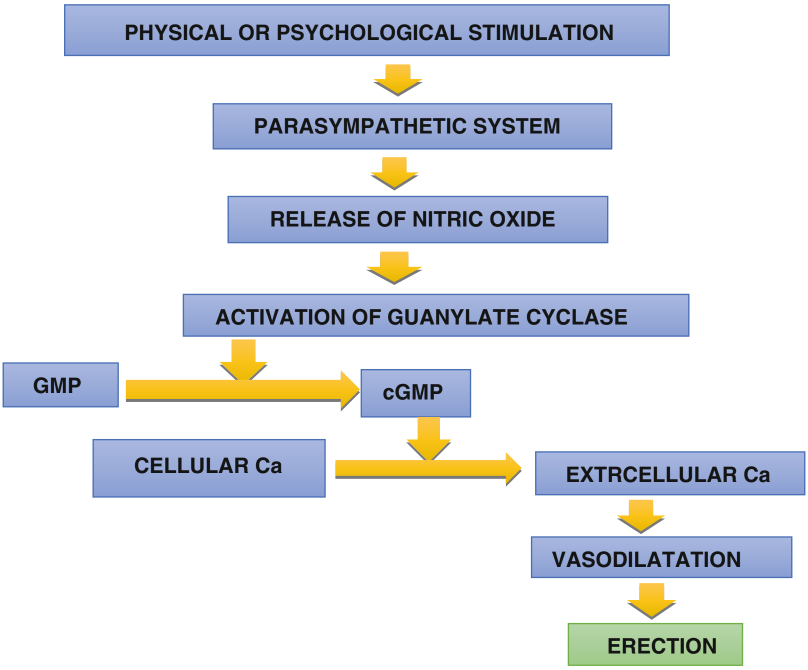


Figs. 23.4 and 23.5 Clinical photograph showing priapism in two children with sickle cell disease

- Factors that can contribute to priapism include the following:
  - Blood disorders including:
    - Sickle cell anemia
    - Leukemia
  - Medications including:
    - Oral medications used to treat erectile dysfunction, such as sildenafil (Viagra), tadalafil (Cialis) and vardenafil (Levitra)
    - Drugs injected directly into the penis to treat erectile dysfunction, such as papaverine
    - Antidepressants, such as fluoxetine (Prozac) and bupropion (Wellbutrin)
    - Drugs used to treat psychotic disorders, such as risperidone (Risperdal) and olanzapine (Zyprexa)
    - Anticoagulant, such as warfarin (Coumadin) and heparin
    - Alcohol and drug abuse (marijuana or cocaine)
  - Trauma or injury to the genitals, pelvis or the perineum is a cause of nonischemic (high flow) priapism
  - Other causes of priapism include:
    - Spinal cord injury
    - Blood clots
    - Poisonous venom, such as venom from scorpions or black widow spiders

23.3 Etiology

- Priapism can be idiopathic or can be secondary to a variety of diseases, conditions, or medications.
- In the United States, the most common cause of priapism in the adult population involves agents used to treat erectile dysfunction.
- Internationally, most cases are idiopathic.
- The most common cause of priapism in the pediatric population is sickle cell disease (SCD), which is responsible for more than 65 % of cases.
- Leukemia, trauma, and idiopathic causes are the causes in 10 % of patients.
- Pharmacologically induced priapism is the etiology in 5 % of children.
- Among the secondary causes of low-flow priapism are the followings:
  - Sickle cell anemia – One study found that, in unscreened children with SCD, priapism was the first presentation in 0.5 % of cases.
  - Thalassemia
  - Dialysis
  - Vasculitis
  - Fat embolism (from multiple long-bone fractures or intravenous infusion of lipids as part of total parenteral nutrition)



- Neurologic diseases that can result in low-flow priapism include the following:
  - Spinal cord stenosis (i.e. trauma to the medulla)
  - Autonomic neuropathy and cauda equina compression
- Neoplastic disease (metastatic to the penis or obstructive to venous outflow) that can result in low-flow priapism include the following:
  - Prostate cancer
  - Bladder cancer (highest risk)
  - Hematologic cancer (leukemia)
  - Renal carcinoma
  - Melanoma
- Pharmacologic causes of low-flow priapism include the following:
  - Intracavernosal agents – Papaverine, phentolamine, prostaglandin E1
  - Intraurethral pellets (i.e. medicated urethral system for erection with intracavernosal prostaglandin E1)
  - Antihypertensives – Ganglion-blocking agents (e.g. guanethidine), arterial vasodilators (e.g. hydralazine), alpha-antagonists (e.g. prazosin), calcium channel blockers
  - Psychotropics – Phenothiazine, butyrophenones (e.g. haloperidol), perphenazine, trazodone, selective serotonin reuptake inhibitors (e.g. fluoxetine, sertraline, citalopram) [3]
  - Anticoagulants – Heparin, warfarin (during rebound hypercoagulable states)
  - Recreational drugs – Cocaine
  - Hormones – Gonadotropin-releasing hormone (GnRH), tamoxifen, testosterone, androstenedione for athletic performance enhancement
  - Herbal medicine – *Ginkgo biloba* with concurrent use of antipsychotic agents
  - Miscellaneous agents – Metoclopramide, omeprazole, penile injection of cocaine, epidural infusion of morphine and bupivacaine
  - Only rare case reports have associated phosphodiesterase-5 enzyme inhibitors such as sildenafil with priapism. In fact, several reports suggest sildenafil as a means to treat priapism and as a possible means of preventing full-blown episodes in patients with sickle cell disease.

- High-flow priapism may result from the following forms of genitourinary trauma:
  - Straddle injury
  - Intracavernous injections resulting in direct cavernosal artery injury
- Rare causes of priapism include the following:
  - Amyloidosis (massive amyloid infiltration)
  - Gout (one case report)
  - Carbon monoxide poisoning
  - Malaria
  - Black widow spider bites
  - Asplenia
  - Fabry disease (rare association, occasionally noted to be priapism of the high-flow type)
  - Vigorous sexual activity
  - *Mycoplasma pneumoniae* infection (mechanism is thought to be a hypercoagulable state induced by the infection)

23.4 Classification of Priapism

- Priapism is a sustained painful erection of the penis often nocturnal or starting in the early hours of the morning.
- Priapism develops when there is excess arterial inflow to the penis or when there is persistent venous outflow obstruction to the penis.
- Priapism is classified into two main types:
  - High flow arterial priapism. This is also called non-ischemic priapism.
  - Low flow priapism. This is also called ischemic priapism.
- High flow (non-ischemic) priapism:
  - This is usually seen following trauma causing injury to the cavernosal artery.
  - This type of priapism is generally not painful and may manifest in an episodic manner.
  - The penis in high flow priapism is neither fully rigid nor painful and does not require an emergency treatment.
  - Characteristics of high-flow priapism include the following:
    - High flow priapism is characterized by an increase of arterial supply to the corpora cavernosa while the venous drainage remains normal.
    - An adequate arterial flow and well-oxygenated corpora
    - The prognosis is better, and secondary impotence is rare (<20 %).
    - In children high flow priapism is typically caused by post-traumatic arterio-cavernosal fistula (from penile, perineal or pelvic trauma), and generally manifests several days after the trauma.
    - Evidence of blunt or penetrating injury to the penis or perineum especially straddle injury is usually the initiating event.
    - It can also be caused by:
      - Intracavernosal injections of vasoactive agents
      - Scorpion or snake bites
      - Substance abuse (mainly cocaine, which can cause high or low output priapism)
      - Therapeutic drugs (especially psychiatric medications with autonomic nervous system effects
      - Infectious diseases or tumors
- Low flow priapism (ischemic):
  - This is the commonest type
  - Low flow priapism is characterized by loss of vascular regulation.
  - Venous drainage is impaired, presumably as a consequence of vascular blockage by deformed red blood cells.
  - This is the classic type seen in patients with SCD where there is stasis leading to hypoxia and acidosis of venous blood in a normally erected penis. This will lead to sickling of RBCs within the corpora cavernosa venous sinusoids, venous outflow obstruction and engorgement of the corpora cavernosa. The corpora spongiosa and glans of the penis are spared.
  - The corpora cavernosa becomes rigid and tender to palpation.
  - This may be further complicated as the fixed resistance maintained by the adventitia of the corpora cavernosa causes a compartment syndrome.

  - Low-flow priapism is generally painful, although the pain may disappear with prolonged priapism.
  - Characteristic features of low-flow priapism include the following:
    - Rigid erection
    - Ischemic corpora as indicated by dark blood upon corporeal aspiration
    - No evidence of trauma
  - Low flow priapism is considered a medical and surgical emergency and priapism should be resolved within 6 h of the onset of the episode to minimize the sequelae.
  - In addition to SCD, low flow priapism can be caused other hematologic diseases with hypercoagulability or hyperviscosity such as leukemia's and several drugs.
- It is important to differentiate between these two types as the management and prognosis are different.
- The two types of priapism can be differentiated using color duplex Doppler ultrasonography and analysis of blood aspirated from the corpora cavernosa.
  - Color Doppler ultrasonography measures blood flow. This typically show little or no blood flow in the cavernosal arteries in those with low flow priapism.
  - Analysis of blood aspirated from the corpora cavernosa is done at the time of aspiration and irrigation.
  - In patients with high flow priapism, the aspirated blood:
    - Is bright red
    - Has a pO_2 >90 % mmHg, pCO_2 <40 mmHg and a pH of approximately 7.40.
  - In patients with low flow priapism, the aspirated blood:
    - Is dark in color
    - Has a pO_2 <30 mmHg, pCO_2 >60 mmHg and a pH <7.25.
- Priapism is also classified into two types:
  - Stuttering priapism: This lasts 2–4 h, often recurrent and may precede a severe attack.
  - Acute (Severe) priapism: This lasts longer than 4 h and can result in impotence.

23.5 Clinical Features

- Priapism causes abnormally persistent erections not related to sexual stimulation.
- Priapism symptoms may vary depending on the type of priapism.
- There are two main types of priapism: ischemic and nonischemic priapism.
- Ischemic priapism:
  - Ischemic, also called low-flow, priapism is the result of blood stasis in the penis.
  - It's the more common type of priapism.
  - Low-flow, ischemic-type priapism is generally painful, although the pain may disappear with prolonged priapism.
  - It is characterized by ischemic corpora, as indicated by dark blood upon corporeal aspiration; and no evidence of trauma
  - The history may reveal an underlying cause
  - Stuttering priapism is unwanted erection off and on for several hours.
  - Signs and symptoms include:
    - Unwanted erection lasting more than 4 h
    - It is characterized by a rigid, painful erection
    - Rigid penile shaft, but usually soft glans of penis
    - Usually painful or tender penis
- Nonischemic priapism:
  - Nonischemic, or high-flow, priapism occurs when too much blood flows into the penis.
  - This type of priapism is associated with blunt or penetrating injury to the perineum. It may manifest in an episodic manner.
  - Nonischemic priapism is usually painless.
  - Signs and symptoms include:
    - Unwanted erection lasting at least 4 h
    - Erect but not rigid penile shaft
    - Patients with high-flow priapism typically have a history of blunt or penetrating trauma to the penis or perineum, resulting in a fistula between a cavernosal artery and the corpus cavernosum.
    - Clinically, high-flow priapism is characterized by a painless erection; tumescence is typically less marked than in low-flow priapism.

    - The presence of bright red blood during aspiration is a helpful but not pathognomonic finding of high-flow priapism.
    - Penile blood gases findings approximate normal arterial values.
    - Penile duplex ultrasonography with angiographic confirmation helps to identify and locate these fistulae.
- Patients with priapism report a persistent erection.
- The physical examination detects an erection restricted to the corpora cavernosa. The spongiosum and the glans remain flaccid, except for the rare cases of tricorporal priapism.
- Because of the lack of involvement of the periurethral spongiosum, there are normally no micturating problems.
- Accompanying symptoms depend on the type of priapism and the duration of engorgement.
- Penile priapism generally involves only the paired corpora cavernosa, with the glans and corpora spongiosum remaining flaccid or softly distended without rigidity.
- In high flow priapism the erection is less rigid and the penis is pink and pulsatile.
- There can be signs of trauma (hematomas, bruises).
- It may be possible to resolve the erection compressing the arteriovenous fistula feeder vessel, but the erection will recur immediately after the compression is withdrawn.
- In low flow priapism the penis is rigid, extremely painful and seems ischemic: it does not pulse, is pale or grayish and cold. These manifestations are more evident after the episode has evolved for at least 4 h.
- In young children, the presence of the Piesis sign (prompt detumescence upon perineal compression with the examiner's thumb) indicates high-flow priapism.
- To provide appropriate treatment, physicians must differentiate between low-flow and high-flow priapism. This is accomplished by taking a thorough history, performing a careful physical examination, and measuring the oxygen content of blood within the corpora cavernosa by penile blood gas analysis.

23.6 Investigations

- A complete blood cell count (CBC) should be performed to determine whether the patient has anemia, leukocytosis, or thrombocytosis.
- Patients with sickle cell disease should have a CBC and a reticulocyte count.
- If sickle cell status is unknown, a hemoglobin electrophoresis should be done.
- Patients with sickle cell disease may also need a blood type and screen performed in case blood transfusion or exchange is necessary.
- Urinalysis and urine culture
- Measurement of plasma thromboplastin or activated partial thromboplastin time to determine coagulation status may be useful, as priapism may require surgical intervention if medical treatment fails.
- Penile blood gas results allow differentiation between high- and low-flow priapism.
  - Low-flow priapism, penile blood gases findings:
    - The blood will be dark
    - Acidotic (pH <7.0)
    - Hypercarbonic (PCO >60 mmHg)
    - Hypoxemic (PO_2 <30 mmHg)
    - Variations in these values depend on the duration of priapism.
  - High-flow priapism penile blood gases findings:
    - The blood will be red
    - Alkalotic (pH >7.0)
    - Normally oxygenated (pO_2 >60 mmHg)
    - pCO_2 <70 mmHg
- Color-flow penile Doppler imaging is currently the study of choice to differentiate high-flow from low-flow priapism. In patients with high-flow priapism, ultrasonography can help identify and locate fistulas.
- In patients with high-flow priapism, selective penile angiography may be required in order to identify the site of the fistula, or to confirm the location of a fistula identified by ultrasound. The fistula can then be closed by embolization.
- Perform chest radiography or computed tomography (CT) scanning if the history is consistent with a malignant or metastatic condition.

- Use of scintigraphy has been proposed to differentiate low (decreased uptake, “cold” CC) from high flow cases, but the limited availability of the test, its low specificity and sensitivity and the lack of a comparative or gold standard has limited its use.
- Doppler ultrasound is more useful for high flow cases, to identify an arteriovenous fistula supplying the erection.
- Cavernosography is rarely used, because blood analysis is adequate and less aggressive.
- Arteriography of the internal pudendal artery has some limited use in high flow cases in which there is an intention to treat by embolization or surgery.

23.7 Management

- Appropriate treatment of priapism varies, depending on whether the patient has low-flow or high-flow priapism.
- Most priapism cases are the low-flow ischemic type.
- Treatment of low-flow priapism should progress in a stepwise fashion, starting with therapeutic aspiration, with or without irrigation, or intracavernous injection of a sympathomimetic agent.
- Treatment of high-flow priapism focuses on identification and obliteration of fistulas.
- In patients with priapism secondary to other disorders, attempt to treat the underlying condition whenever possible.
- Treatment for priapism secondary to sickle cell disease includes hydration, alkalization, analgesia, and oxygenation to prevent further sickling. Hypertransfusion and/or exchange transfusions may be required to increase hemoglobin concentration to higher than 10 % and decrease hemoglobin S to less than 30 %.
- At least 50 % of patients with priapism have persistent impotence, either because of the priapism event or its treatment.
- The European Association of Urology guidelines on the diagnosis and treatment of priapism include:
  - Interventions for ischemic priapism, which is an emergency condition, should begin within 4–6 h and include decompression of the corpora cavernosa by aspiration and intracavernous injection of sympathomimetic drugs
  - When conservative management for ischemic priapism fails, surgical treatment is recommended
  - For patients with long-lasting priapism, immediate implantation of a prosthesis should be considered
  - For arterial priapism, which is not an emergency, selective embolization has high success rates
  - The main therapeutic goal for stuttering priapism is prevention of future episodes, which may be achieved pharmacologically (although information on the efficacy of such treatment is limited)
  - Prehospital Care
- Prehospital Care:
  - Any patient who has an erection for longer than 4 h, especially if he has a predisposing illness (e.g., sickle cell disease) should receive therapy for priapism
  - Most cases, if seen early enough in their course, respond to conservative measures.
    - The use of ice packs to the perineum and penis
    - Ask the patient to walk upstairs. The latter strategy is thought to work via an arterial steal phenomenon.
    - External perineal compression may also be a useful temporizing measure.
- Low-Flow Priapism
  - Treatment should progress in a stepwise fashion, accompanied by supportive care and the identification and treatment of reversible causes.
  - Intracavernosal phenylephrine (Neo-Synephrine) is the drug of choice and first-line treatment of low-flow priapism

because the drug has almost pure alpha-agonist effects and minimal beta activity.

  - In short-term priapism (<6 h), especially drug-induced cases, intracavernosal injection of phenylephrine alone may result in detumescence.
  - Some studies suggest that terbutaline orally, at a dose of 5–10 mg, followed by another 5–10 mg 15 min later, if required, produces resolution in about one third of patients.
  - Oral pseudoephedrine, 60–120 mg orally has also been suggested as a potential therapy due to its alpha-agonist effect. The exact efficacy of this medication orally is unknown.
  - Oral medications may be a reasonable treatment option to use while preparing for aspiration/injection. If no resolution occurs within 30 min, injection therapy is required.
  - Aspiration/injection of the corpus cavernosum:
    - First perform a penile nerve block.
    - Inject around the entire base of the penile shaft with 1 % lidocaine without epinephrine or bupivacaine without epinephrine.
    - Providing anesthesia will increase patient comfort and improve patient cooperation with the sometimes-painful penile aspiration procedure.
    - After anesthesia is ensured, use a 19-gauge needle attached to a large syringe to puncture the corpus cavernosum. The needle should be inserted through the shaft of the penis laterally to avoid the corpus spongiosum and urethra ventrally and the neurovascular bundle dorsally.
    - Aspirate 20–30 mL of blood from either the 2-o'clock or 10-o'clock position while milking the shaft.
    - Aspiration may be difficult because of the sluggish blood within the corpus cavernosum.
    - Saline irrigation and repeated aspirations may improve flow dynamics.
    - Because multiple communications exist from one corpus to the other, aspiration usually is required on one side only.
    - If initial aspiration of the corpus cavernosum reveals bright red blood rather than dark venous blood, consider an arterial cause for priapism and treat as for high-flow cases.
    - Aspiration alone has a success rate of around 30 %.
    - If this procedure is not successful, phenylephrine, epinephrine, or methylene blue may be instilled into the corpus cavernosa.
    - For the injection, use a mixture of 1 ampule of phenylephrine (1 mL: 1,000 mcg) and dilute it with an additional 9 mL of normal saline.
    - Using a 29-gauge needle, inject 0.3–0.5 mL into the corpora cavernosa, waiting 10–15 min between injections.
    - Monitor vital signs and apply compression to the area of injection to help prevent hematoma formation.
    - If phenylephrine is not available, epinephrine can be used. However, epinephrine has more adverse effects and is considered second-line treatment. Another second-line treatment is instillation of methylene blue.
    - Alternatively, the corpora cavernosa can be irrigated with a diluted solution of phenylephrine. A diluted solution can be infused 10–20 mL at a time.
    - If aspiration or injection is successful in producing detumescence, place an elastic bandage around the shaft of the penis to ensure continued emptying of the corpora and to compress the puncture site.
- High-Flow Priapism:
  - Acutely, observation alone may be sufficient for high-flow priapism, because many cases resolve spontaneously, and even with prolonged priapism these patients are unlikely to experience significant pathological damage or impaired erectile function.

  - Compression therapy may be successful in certain cases, especially children; continuous compression may be maintained with a strap-on dressing.
  - Selective angiography with subsequent embolization of the offending vessel has been shown to be effective with few long-term complications in some studies.
  - Selective arterial embolization can be done using autologous blood clot, gelatin sponge, microcoils, or chemicals.
  - Patients who do not respond to more conservative measures may benefit from this approach.
  - Surgical ligation of the fistula may be required. However, potential complications of this procedure include long-term impotence.
- Surgical Care:
  - A transglanular-to-corpus cavernosal scalpel or needle-core biopsy (Ebbehoj or Winter technique) is the first reasonable approach for refractory priapism.
  - A unilateral shunt is often effective.
  - Bilateral shunts are used only if necessary (usually apparent after 10 min).
  - The El-Ghorab procedure is a more aggressive open surgical cavernosal shunt and is indicated if the Winter shunt fails.
  - Quackel shunts are cavernosal-spongiosum shunts (unilateral or bilateral) and are performed via a perineal approach. Such shunts are rarely effective if a more distal shunt has already failed (e.g., El-Ghorab procedure) because thrombosis of the corpora is usually already present.
  - A Grayhack shunt is a cavernosal-saphenous vein shunt (rarely necessary or indicated). Proximal cavernosal-saphenous shunt (Grayhack shunt) surgically connects the proximal corpora cavernosum to the saphenous vein.
  - Prolonged low-flow priapism results in a variable degree of cavernosal fibrosis and a subsequent loss of penile length.
  - The delayed insertion of a penile prosthesis can be difficult, with high complication rates.
  - Immediate insertion of a penile prosthesis in patients with prolonged low-flow priapism is simple and maintains penile length. This may be offered to patients at initial presentation, as the complication rate is low and the subsequent outcome excellent.

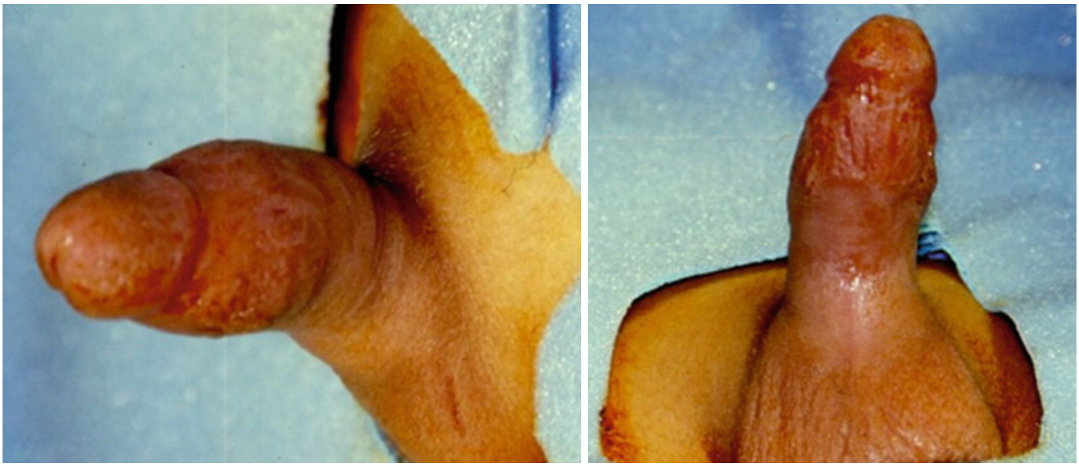
23.8 Prognosis

- The prognosis depends on the duration of symptoms, the patient's age, and the underlying pathology.
- The duration of symptoms is the single most important factor affecting outcome.
- A Scandinavian study reported that 92 % of patients with priapism for less than 24 h remained potent, while only 22 % of patients with priapism that lasted longer than 7 days remained potent.
- All patients with priapism should be warned about the long-term risk of erectile dysfunction.
- In general, low flow (ischemic) priapism poses a higher risk of impotence than high-flow arterial priapism.
- Sickle cell disease patients appears to be particularly at increased risk.
- A study by Anele and Burnett found that patients with sickle cell disease who experience even minor episodes of recurrent ischemic priapism are five times more likely to develop erectile dysfunction compared with non–sickle cell patients.
- Infection can complicate priapism.
- Patients must understand that a poor outcome is possible despite appropriate and timely management.
- Stuttering priapism requires careful counselling for episodic management.
- Chronic prophylaxis may be obtained using α-adrenergic sympathomimetics, phosphodiesterase type 5 inhibitors and, in sickle cell disease, hydroxyurea.

23.9 Priapism and Sickle Cell Disease

23.9.1 Introduction

- Priapism is defined as a prolonged sustained erection, often accompanied by pain and swelling, and not associated with sexual desire.
- Priapism is one of the serious complications of sickle cell disease (SCD) and if left untreated, irreversible fibrosis and impotency may occur (Figs. 23.6 and 23.7).
- The exact incidence of priapism in patients with sickle cell disease is not known but it was thought to be present in 5–10 % of the patients.
- In patients with SCD, the probability of having at least one episode of priapism by age 20 was reported to be 89 %.
- Approximately 27 % of patients with SCD reported having at least one episode of priapism.
- The mean age of patients when they had their first episode was 12 years, and the majority of episodes were nocturnal.
- The frequency of priapism in adults ranges from 30 to 45 %.
- There also appears to be bimodal peak frequencies for patients 5- to 13-years old and 21- to 29-years old.
- Although the mechanism that causes low-flow priapism in patients with SCD is not fully understood, it may be caused by the sickling of red blood cells in the sinusoids of the corpora cavernosa during normal erection. This sickling leads to venous stasis, resulting in decreased local oxygen tension and pH, which further potentiate stasis, sickling, and secondary priapism.
- This type of priapism is considered a medical and surgical emergency because, if it is left untreated, irreversible cellular damage and fibrosis may occur, resulting in long term impotence.
- There are two types of priapism:
  - Low flow priapism (Ischemic priapism)
  - High flow priapism (Nonischemic priapism)
- Low-flow priapism tends to be much more common in patients with SCD.
- High-flow priapism is thought to be secondary to unregulated arterial inflow, leading to prolonged but painless erection. It is more commonly associated with penile trauma, but it has been reported in patients with SCD.
- High-flow priapism tends to require arterial embolization or ligation to produce detumescence, while low-flow priapism tends to respond to pharmacologic agents and or surgery.



Figs. 23.6 and 23.7 Clinical photographs showing priapism in a child with sickle cell disease

- Priapism in patients with SCD can be acute, lasting for hours or days, or stuttering, occurring in an intermittent pattern, lasting for a few minutes to up to 3 h and generally resolving on its own.

23.9.2 Epidemiology

- Priapism has been described at nearly all ages, from infancy through old age.
- A bimodal distribution has been noted, with peaks at 5–10 years and 20–50 years.
- Internationally, the overall incidence of priapism is 1.5 cases per 100,000 person-years.
- In men older than 40 years, the incidence increases to 2.9 cases per 100,000 person-years.
- Cases in younger groups are more often associated with SCD, while those in older groups tend to be secondary to pharmacologic agents.
- The rate of priapism in adults with SCD is as high as 89 %.
- In one study, 38–42 % of adult patients with SCD reported at least one episode of priapism.
- The rate of priapism among children with SCD is as high as 27 %.
- Approximately two thirds of all pediatric patients who have priapism also have SCD.
- Priapism of the clitoris has been reported but is extremely rare.

23.9.3 Classification

- Priapism is prolonged painful erection of the penis often starting in the early hours of the morning.
- Priapism develops when there is excess arterial inflow to the penis or when there is persistent venous outflow obstruction to the penis.
- Two types of priapism exist based on blood flow patterns in the penis:

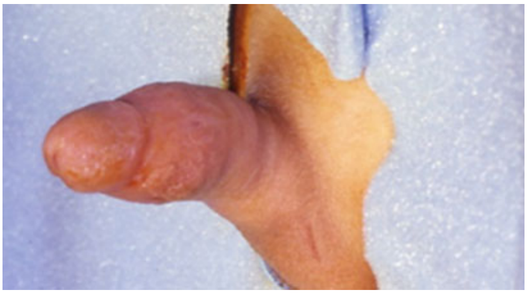


Fig. 23.8 A clinical photograph showing low flow priapism in a child with sickle cell disease

  – Low-flow priapism:
    - This occurs when there is decreased outflow from penile veins, leading to venous hemostasis.
    - Intracavernosal blood sampling reveals acidosis and decreased oxygen tension.
    - Although the mechanism that causes low-flow priapism is not fully understood, it may be caused by the sickling of red blood cells in the sinusoids of the corpora cavernosa during normal erection.
    - This sickling leads to venous stasis, resulting in decreased local oxygen tension and pH, which further potentiate stasis, sickling, and secondary priapism.
    - This type of priapism is considered a medical emergency because, if it is left untreated, irreversible cellular damage and fibrosis may occur, resulting in impotence.
    - Low-flow priapism tends to be much more common in patients with SCD (Fig. 23.8).

  – High-flow priapism:
    - This is thought to be secondary to unregulated arterial inflow, leading to prolonged but painless erection.
    - It is more commonly associated with penile trauma, but it has been reported in patients with SCD.
    - Diagnosis can often be made by simple observation (erect, painless, brightly colored penis) and aspiration of bright red cavernosal blood.

    - Since this type of priapism is associated with the presence of a large amount of oxygenated blood, fibrosis and cellular damage do not occur, and treatment can occur on an elective rather than emergent basis.
    - It is important to distinguish between high- and low-flow priapism, because treatment strategies differ depending on the type of priapism present.
    - High-flow priapism tends to require arterial embolization or ligation to produce detumescence, while low-flow priapism tends to respond to pharmacologic agents.
- Priapism in patients with SCD is also classified into two types based on onset:
  - Acute severe priapism:
    - This lasts longer than 4 h and can result in impotence.
  - Stuttering priapism:
    - This occurs in an intermittent pattern, lasting for a few minutes to up to 3 h
    - Generally it resolve on its own
    - It is often recurrent and may precede a severe attack
    - Stuttering or recurrent priapism may occur in patients with sickle cell trait or disease.
    - Usually self-limiting in nature, over time such episodes may lead to erectile dysfunction.

23.9.4 Pathophysiology

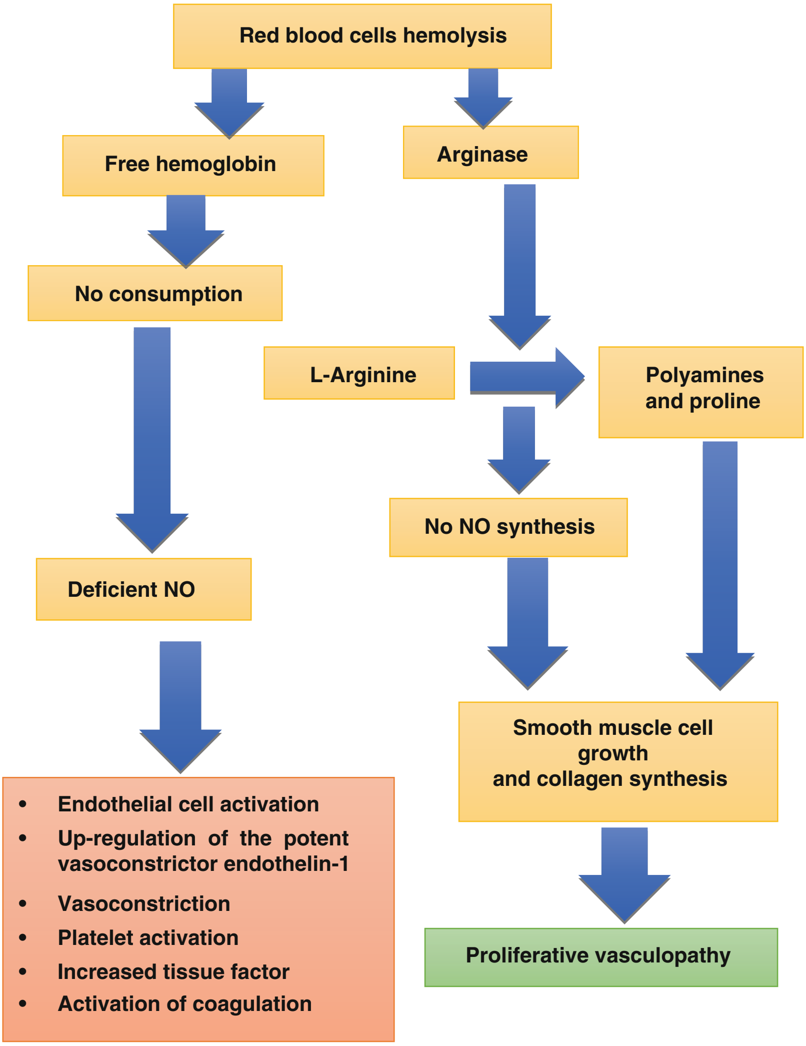
- Anatomically, the penis is composed of two corpora cavernosa and one corpus spongiosum.
- The two corpora cavernosa are made up of smooth muscles and covered in a tunica albuginea. This is made up of two layers, an inner layer that supports the cavernous tissue and an outer layer that runs longitudinally from the glans to insert onto the pubic rami.
- The inner and outer layers of the tunica albuginea are connected by emissary veins.
- The corpus spongiosum on the other hand has no tunica albuginea, and therefore, serves as an arteriovenous fistula with less rigidity than the corpora cavernosa. The urethra runs within the corpus spongiosum.
- Normally, erection results from corporal smooth muscle relaxation secondary to the release of neurotransmitters.
- The principal neurotransmitter for erection is nitric oxide (NO), which is released by both nerve terminals and endothelial cells. The NO then diffuses into both trabecular cells and arterial smooth muscle cells. This activates guanylate cyclase, which catalyzes the formation of cGMP from GTP, and results in a cascade that decreases intracellular calcium and opens potassium channels to cause smooth muscle relaxation.
- This result in increased blood flow and filling of the corpora cavernosa sinusoids with blood and ultimate compression of venous outflow and trapping of blood.
- Alternative pathways generate cAMP, which enhances this effect.
- Detumescence follows degradation of cGMP and cAMP. cGMP is degraded by phosphodiesterase-5 (PDE5).
- Typically, in priapism, the corpora cavernosa are tense, congested and tender to palpation while the glans and corpus spongiosum are usually soft and uninvolved.
- Stasis and low blood flow rates within the sinusoids of the erectile tissue make the penis a site at high risk for developing a veno-occlusive crisis in patients with SCD.
- SCD is genetically determined by a mutation in the β-globin chain of hemoglobin.
- It results from a single change of one amino acid, valine for glutamic acid in the sixth position of the beta chain of hemoglobin.
- This results in a change in hemoglobin from hemoglobin A to hemoglobin S which is known to be associated with increased mortality and morbidity including pulmonary hypertension, cerebral vascular accidents, lower extremity ulcerations, osteonecrosis, painful

crises, and priapism among other less common clinical problems.
- Classically, in priapism, the primary mechanism is thought to be obstruction of venous drainage resulting in viscous, hypoxic blood leading to interstitial edema and fibrosis of the corpora cavernosa, ultimately resulting in impotence.
- It was shown that the length of time of ischemia directly correlates with the likelihood of return of erectile function, and therefore, ischemic priapism is considered a urologic emergency.
- It was shown that all patients with ischemic priapism episodes of greater than 12 h duration had reduction in erectile function and no patients with priapism lasting greater than 36 h had return of spontaneous erectile function.
- Priapism in sickle cell patients has been classically attributed to vaso-occlusion episodes.
- The deformed sickled red blood cells leads to vasooclusion which is precipitated to by hypoxemia and acidosis in the corpora cavernosa (caused by vasoconstriction, hypovolemia or stasis in the corpora cavernosa during physiologic erection).
- This cause microvascular obstruction, in a vicious cycle: red cells sickling causes vascular obstruction and secondary ischemia, which promotes new red cells sickling.
- This however is not the case and currently, the more accepted theory is the inflammatory theory which is based on the mediating function of the vascular endothelium in the microcirculation.
- In patients with SCA, several factors contribute to the development of priapism including anatomic factors and a low-flow state.
- Recently however it was shown that nitric oxide (NO) plays an important role in the pathogenesis of priapism in these patients.
- SCD is characterized by hemolysis, the extent of this is variable.
- The hemolysis leads to the release of the highly oxidative group heme and causes degradation of the cellular membrane, releasing hemoglobin and arginase into the extracellular environment. This is more exacerbated in those with functional asplenia (autosplenectomy) or surgical asplenia following splenectomy.
- Free hemoglobin oxidizes into methemoglobin, liberating heme groups and ferrous ions.
- Freed arginase in the extracellular environment consumes L-arginine, a substrate for the endothelial synthesis of nitric oxide.
- Nitric oxide is directly consumed in the oxidation of hemoglobin to methemoglobin and in the neutralization of heme groups and ferrous ions.
- The oxidative lesion, direct consumption and deficit of nitric oxide synthesis cause endothelial activation, release of inflammatory and thrombogenic factors and a tendency to vasoconstriction.
- Permanent vascular injuries occur over the long term, perhaps fostered by chronic tissue hypoxemia and the synthesis of vasoproliferative substances.
- Secondary or simultaneous sinusoidal blockage by deformed red blood cells in the microcirculation and worsening of the local process of hemolysis may occur.
- RBC hemolysis result in the release of cell-free plasma hemoglobin which scavenges available NO.
- The absence of NO leads to:
  - Increased vascular tone
  - Platelet activation
  - Up regulation of vascular adhesion molecules.
- Reduced levels of NO have been implicated in the pathogenesis of pulmonary hypertension, priapism and leg ulcers in patients with SCA.
- NO is an important smooth muscle relaxant and a potent vasodilator. It mediates this

through increasing levels of cyclic GMP (cGMP). This results in smooth muscle relaxation, vasodilatation of penile arteries, increased blood flow and penile erection. This effect is regulated by phosphodiesterase type 5 (PDE-5) which degrades cGMP.
- SCA patients have elevated free hemoglobin concentrations compared to normal volunteers as a result of hemolysis. This will result in increase in NO scavenging with subsequent prevention of vasodilation.
- Other associated risk factors for priapism include Lactate dehydrogenase (LDH), bilirubin and reticulocyte count which are elevated in patients with SCA and priapism.
- Chronic scavenging of NO results in a decreased expression of downstream regulatory molecules including PDE5 that normally degrades cGMP, the second messenger in NO signaling.
- The combination of chronically decreased PDE5 and normal cGMP generation following nerve stimulation may result in an unregulated, prolonged erection.
- In patients with SCA, there is:
  - Reduction in NO bioavailability
  - A significant down regulation of PDE-5
  - Uncontrolled cGMP activity.
  - Elevated levels of adenosine in the penis may also contribute to the pathogenesis of priapism but this has not been well established.
- Risk factors for priapism in SCA patients include:
  - Prolonged sexual activity
  - Fever
  - Dehydration
  - Exposure to alcohol
  - The use of marijuana
  - The use of cocaine, psychotropic drugs, and testosterone
- In priapism these new concepts have specific implications, as the physiologic mechanisms of erection are specifically controlled by nitric oxide.
- Notably, priapism is more frequent in the severe forms of SCD, with an association to pulmonary hypertension (up to five times more common than in other SCD patients) and strokes.
- Episodes of priapism are also linked to a rise in serum markers of hemolysis, such as increase of reticulocytes, indirect bilirubin, and lactate dehydrogenase (LDH).

23.9.5 Clinical Features

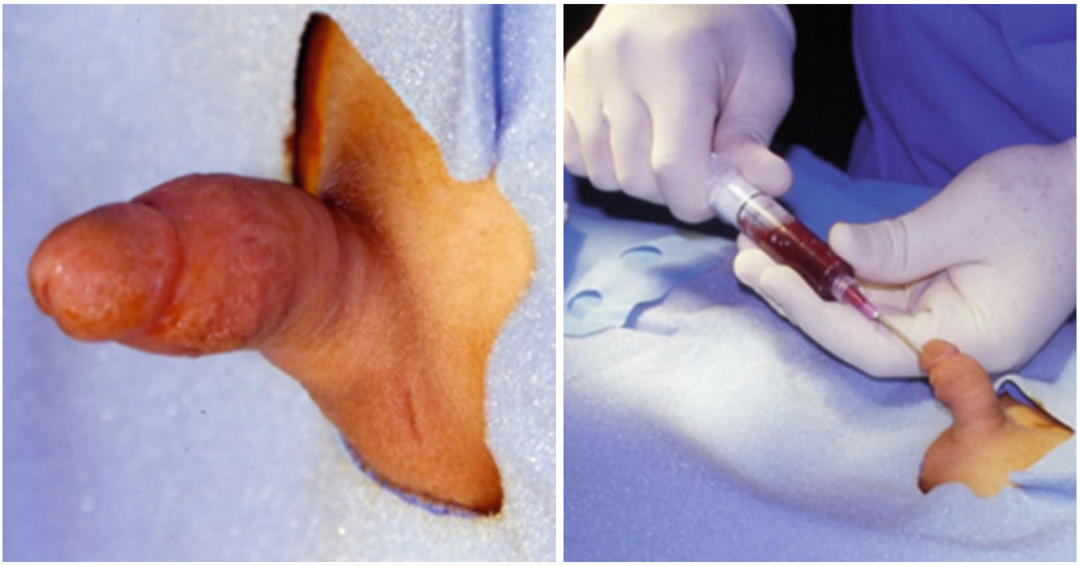
- Priapism may occur at any age. The mean age of onset is 12–15 years but has been reported in children.
- 70–90 % of affected patients report their first episode prior to 20 years of age.
- The exact prevalence of priapism is not known but it has been estimated to range from 6 to 45 %.
- Priapism has been reported in various hemoglobinopathies. Commonly it is seen in sickle cell anemia (homozygous sickle cell) but has been reported in patients with hemoglobin SC disease, sickle cell beta thalassemia and rarely in those with sickle cell trait.
- Priapism may occur as an isolated episode or as part of generalized SCA vasoocclusive crisis.


Red blood cells hemolysis
Free hemoglobin
Arginase
No consumption
L-Arginine
Polyamines and proline
No NO synthesis
Deficient NO
Smooth muscle cell growth and collagen synthesis
Endothelial cell activation
Up-regulation of the potent vasoconstrictor endothelin-1
Vasoconstriction
Platelet activation
Increased tissue factor
Activation of coagulation
Proliferative vasculopathy

- Priapism may occur also during sleep or following an active sexual intercourse.
- These patients usually present with an erect painful penis and on palpation, the penis is hard in consistency while the glans penis is soft.
- Many of these patients are not aware of this as a complication of SCA and this leads to delay in seeking medical advice.
- The mean duration of symptoms was reported to range from 6 to 70 h (mean 22 h). Some of these patients may resort to sexual intercourse in an attempt to relieve the pain.
- Stuttering priapism:
  - An episode of priapism lasting more than a few minutes but less than 3 h.
  - Stuttering priapism typically occur in clusters, approximately two to three times per week for several weeks.
  - About 60 % of those who develop stuttering priapism will develop an attack of acute priapism in the future.
- The majority of patients with SCD report intermittent episodes preceding an acute episode.
- This emphasizes the need to investigate stuttering episodes in sickle cell outpatients, in order to actively prevent acute episodes and educate the patients.
- The most common precipitants of priapism are sexual activity (including masturbation), dehydration, fever and exposition to a cold environment.

23.9.6 Treatment

- Priapism is a serious complication of SCD.
- There are no definitive guidelines available for the treatment of SCD-related priapism.
- Although conservative management has commonly been advocated, most experts advocate emergent surgical decompression when conservative management fails.
- Patients with SCD should be educated regarding the need to seek prompt specialized treatment for any episode of priapism that lasts longer than 2 h.
- Numerous therapeutic options have been attempted, including blood transfusion, exchange blood transfusion, diethylstilbestrol, gonadotropin-releasing hormone analogues, various adrenergic agonists, and hydroxyurea.
- Few agents have actually been examined in a controlled clinical trial, making it difficult for practitioners to treat this complication.
- The parents of children with SCD should be educated about priapism and how to treat it initially.
- Some educated and willing parents could also be taught how to aspirate the cavernosa and then inject intracavernosal epinephrine or phenylephrine for prolonged episodes or for those not relieved with oral pseudoephedrine.
- It is recommended that treatment should be conservative initially.
- The patient is encouraged to drink extra fluids, urinate, exercise, and take oral analgesics. These simple measures have occasionally been sufficient enough to produce detumescence.
- If the episode of priapism persists beyond 2 h, the patient should report to the emergency department.
  - The patient is assessed clinically
  - The patient should be started on intravenous fluids at 1.5 their maintenance requirements.
  - The patient should be given analgesics to relive the discomfort and pain.
  - Anxiolytics, such as lorazepam, midazolam, or hydroxyzine pamoate, and supplemental oxygen may also be given if needed.
- If priapism persists beyond 4 h, intracavernosal blood aspiration and instillation of an α-agonist should be performed under local or regional anesthesia and repeated as needed.
- Alpha-agonists act as vasoconstrictors and are thought to induce contraction of the smooth muscle of the penile arteries of the corpora cavernosa, forcing blood out of the corpora cavernosa and into the venous system.
- Beta-agonists, on the other hand, act as vasodilators by blocking β-receptors, resulting in smooth muscle relaxation of the vasculature. This allows oxygenated arterial blood to enter the cavernosa, washing out stagnant, already damaged sickle cells.
- Various adrenergic agonists have been used in the treatment of priapism, including:
  - Pure α-agonists (e.g., metaraminol)
  - Mixed α- and β-agonists (e.g., etilefrine, phenylephrine, and epinephrine)
  - Pure β-agonists (e.g., terbutaline)
  - Etilefrine is the ideal α-agonist to use
  - Phenylephrine (preferable, since it is more selective) or epinephrine can be used also.
  - Metaraminol is associated with side effects including transient but severe hypertension.
- The procedure consist of intracavernosal aspiration followed by irrigation with 10 mL of a 1:1,000,000 solution of epinephrine. Aspiration continued until detumescence occurred. If detumescence lasts for at least 30 min, the patient is discharged from the emergency department.
- Others use intracavernosal aspiration and irrigation with diluted epinephrine (20 mL of a solution of 1 mL 1:1,000 epinephrine in 1 L of 0.9 % sodium chloride) are performed.
  - Irrigation and aspiration are performed until sustained detumescence was achieved or a maximum of 200 mL of solution was used, after which an emergency shunt is performed.
  - If irrigation was successful, the patient is observed for 24 h and then discharged home.
- The procedure of aspiration and irrigation (Figs. 23.9, 23.10, 23.11, 23.12, and 23.13):
  - Apply local anesthetic blockade
  - A 21-gauge needle is used for children.



Figs. 23.9 and 23.10 Clinical photographs showing priapism in a child with SCA being treated with aspiration and irrigation

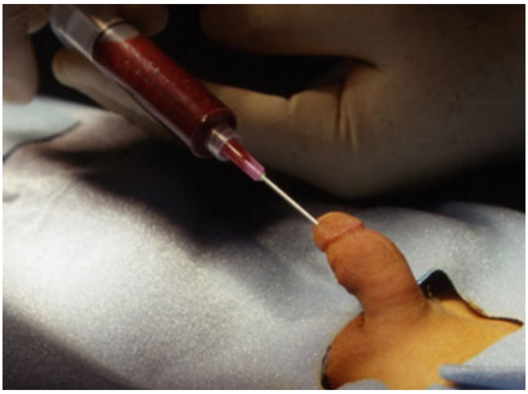


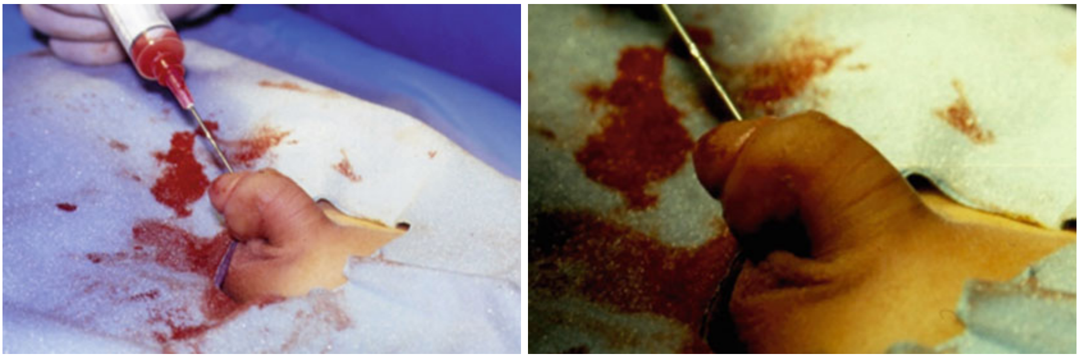
Fig. 23.11 Clinical photograph showing a child with sickle cell disease and priapism being treated with aspiration and irrigation

- Puncture one of the corpora cavernosa, usually via the glans
- In the majority of cases it is not necessary to puncture the two corpora cavernosa.
- Blood should be collected for gas analysis and confirmation of the diagnosis.
- Thereafter the corpora cavernosa are drained.
- Irrigation and drainage of the full extension of the corpora is more efficient.
- The volume of blood removed in the aspiration:
  - This should be limited to a maximum of 7.5 mL/kg (10 % of the blood volume in children >1 year of age), because of the risk of provoking hypovolemia or shock.
- Alpha-adrenergic agonists (etilefrine, phenylephrine, epinephrine, metaraminol) are then injected.
- Injection of adrenergic agents is known to be associated with complications including:
  - Infection
  - Hematomas
  - Urethral injury
  - Fibrosis at the injection site
  - Rarely, penile necrosis.
- The proposed dosages are:
  - 10 ml of adrenaline 1:1,000,000
    - The overall success rate is 87 %
    - A 100 % success was reported in those <24 h duration of priapism
    - In 20 % of cases it was necessary to repeat the injection.
  - Other authors propose diluting 1 mL of adrenaline 1:1,000 solution in 1 L of

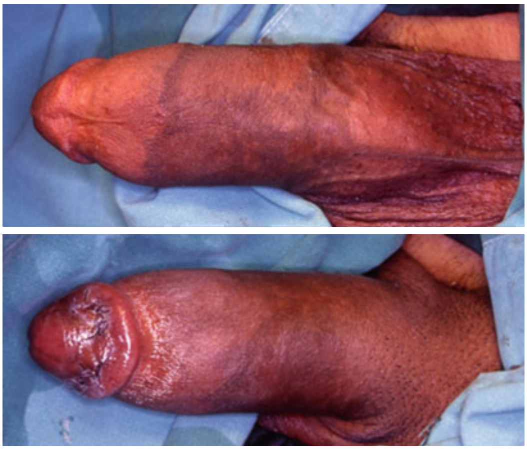
    saline and injecting 20 mL in repeated boluses, until a maximum of ten injections (200 mL).
  - Etilefrine:
    - 5–10 mg per intracavernosal injection, without dilution.
  - All patients who arrive at the emergency department within 36 h of priapism respond to the treatment regimen.
  - Etilefrine can be used to treat priapism in patients with SCD.
  - 5 mg of undiluted intracavernosal etilefrine (if priapism was present for less than 6 h) or aspiration followed by irrigation with intracavernosal etilefrine (if priapism had been present for greater than or equal to 6 h).
- If the priapism continues beyond approximately 12 h, shunt procedure should be considered.
- The shunt procedure should be the last option, as it is associated with higher rates of impotence, and most pediatric patients respond well to pharmacologic treatments.
- To prevent relapse of priapism, patients can be treated with oral etilefrine 0.25 mg/kg twice a day for 1 month.
- Other less commonly used medications to treat priapism include:
  - Phosphodiesterase inhibitors: A single oral dose of 50 mg is used
  - Ketamine injections (0.5–1 mg/kg)
  - Hydralazine
  - Calcium-channel blockers
  - Anticoagulants
  - Corticosteroids
  - Continuous epidural anesthesia
  - Inhaled nitric oxide
- Surgery (Figs. 23.14 and 23.15):
  - Most authors would indicate surgery only in low flow priapism episodes, after 12 h, if conventional medical treatment and injection of the corpora cavernosa with adrenergics could not solve the problem.
  - This can be performed by a distal cavernosa-spongiosum shunt:
    - Winter shunt: This creates a cavernosa-spongiosum shunt by puncturing the glans with a Tru-Cut needle
    - Al-Ghorab shunt: This suture the distal extremity of the corpora cavernosa to the spongiosum into the glans (spongiosum-cavernous anastomoses)
  - Or a proximal shunt:
    - Grayhack shunt: laterolateral spongiosum to proximal penile corpora cavernosa suture
    - A cavernosa-venous diversion to the saphenous vein (saphenous-cavernous) shunts or to the dorsal vein of the penis.
  - The placement of a penile prosthesis should be considered in adulthood, so that patients with erectile dysfunction as a consequence of prior crises can become sexually active.

23.9.7 Prevention of Stuttering Priapism

- Prophylaxis of recurrence of acute episodes or of occurrence of acute episodes in patients with recurrent self-limited priapism include the following therapeutic proposals:
  - First-line treatment should begin with an oral adrenergic agonist, as they seem to have the best efficacy and safety profiles.
  - Etilefrine is the best evidence-supported treatment available.
  - Stuttering priapism is treated with oral etilefrine 0.5 mg/kg for 1 month. A dose is given once every evening in patients with nocturnal priapism or divided into two doses for priapism occurring during the day and at night. The treatment is continued for 1 month after eventual resolution with no recurrence.
  - This can be combined with intracavernosal self-injection in cases of acute episodes lasting more than 1 h.
  - Phenylpropanolamine is an acceptable alternative.
  - Phenylephrine and epinephrine are not available in an orally active formulation.



Figs. 23.12 and 23.13 Clinical photographs showing priapism in a child with SCA being treated with aspiration and irrigation. Note the response to the treatment with resolution of priapism



Figs. 23.14 and 23.15 Clinical photograph showing priapism in an adult with SCA being treated with a distal glans-cavernosal shunt

- Pseudoephedrine is the only preferred oral adrenergic agonist available. It may be given as a once-daily dose at bedtime or as two doses given in the morning and at bedtime
- Terbutaline is an alternative, but it should be considered a second-line therapy behind pseudoephedrine, as there is less evidence supporting its efficacy.
- Other oral agents that may be tried if pseudoephedrine fails include hydralazine, pentoxifylline, and diltiazem, although evidence for the use of these three drugs is weak, and their routine use cannot be fully advocated.
- The third step that should be considered is the use of a gonadotropin-releasing hormone analogue plus flutamide.
  - Leuprolide is the agent of choice.
  - Flutamide should be given initially to minimize the testosterone flare often seen upon initiation of gonadotropin-releasing hormone analogues.
- Hormonal manipulation is also used in the treatment of recurrent priapism.
- Gonadotropin-releasing hormone analogues have fewer risks and adverse effects than those seen with diethylstilbestrol.
- Overall, gonadotropin-releasing hormone analogues appear to be relatively safe and well tolerated by most patients.
- Gonadotropin-releasing hormone analogues also offer the convenience of monthly or quarterly administration rather than the daily or weekly administration needed with oral medications.
- Use of anti-androgenic hormonal manipulation, using gonadotrophin inhibitors (goserelin, leuprolide) or finasteride to reduce androgen levels.
- This treatment, although efficacious, is associated with side effects (loss of libido and erectile function). Those drugs are second- or third-line treatment options.
- Adverse effects have been reported in over 2 % of pediatric patients using leuprolide and include injection-site reactions, generalized pain, rash, and acne. The concern

  with using them in pediatric patients is that sexual maturation may be delayed secondary to the reduction of circulating androgens, which can cause the reproductive organs to return to a prepubertal state.
  - Other agents which may be considered are diethylstilbestrol and hydroxyurea.
    - Diethylstilbestrol is effective but has side effects.
    - Hydroxyurea should decrease the degree of sickling, which is thought to be the major cause of priapism in patients with SCD. However, its adverse effects also limit its use.
  - Diethylstilbestrol:
    - This is used to abort and prevent stuttering priapism.
    - The exact mechanism by which diethylstilbestrol works is unknown.
    - Its use is limited by the recurrence of symptoms 6–8 weeks after discontinuation of the medication and because of the side effects (loss of libido and erectile function, gynecomastia, testicular atrophy).
    - It should be considered a last resort medication, not appropriate for use in pre-pubescent patients.
    - Diethylstilbestrol 5 mg daily for 3–4 days could abort attacks of priapism, and individualized dosages lower than 5 mg daily could be used to prevent priapism.
    - Other adverse effects commonly experienced with diethylstilbestrol include breast tenderness and enlargement, nausea, vomiting, abdominal cramps, headache, dizziness, weight changes, edema, changes in libido, hirsutism, and testicular atrophy.
  - Hydroxyurea:
    - It induces the synthesis of fetal hemoglobin, modifying the mechanisms of endothelial activation and resulting in general improvement of SCD.
    - It may also reduce neutrophil and reticulocyte counts, thereby decreasing the interaction of sickle cells with vascular endothelium resulting in blood “trapping” and, thus, priapism.
    - It is often used to treat patients with SCD who have recurrent pain crises.
    - Hydroxyurea maybe useful in the treatment of sickle-cell-induced priapism.
    - Given the side effects and risks, this approach has been reserved for serious cases.
    - Its adverse effects preclude its use as a first-line drug to treat priapism.
    - Major adverse effects of hydroxyurea include myelosuppression (leukopenia, anemia, and occasionally thrombocytopenia), elevation of hepatic enzymes, gastrointestinal symptoms (nausea, vomiting, diarrhea, constipation, stomatitis, anorexia), renal impairment, fever, chills, malaise, edema, erythema, and rash.
  - There have been case reports describing the isolated but successful use of other pharmacologic agents to induce detumescence in patients with prolonged erection such as ketamine and hydralazine.
  - Methylene blue injected intracavenously has also been reported to be effective in the treatment of priapism. Methylene blue can however cause necrotic abscess.
  - The use of erythrocyte transfusions for 6 months, followed by pentoxifylline for 6 months.
- Blood transfusion:
  - Both simple and exchange transfusions have been used in attempts to increase the hemoglobin and hematocrit, decrease the number of sickled red blood cells, decrease hemoglobin S levels, and increase the number of oxygenated, normal erythrocytes.
  - Exchange transfusions have been questioned for three main reasons:
    - Absence of good quality scientific evidence of its efficacy.
    - The well-known risks associated with transfusion.
    - Availability of blood and difficulties in obtaining blood for emergency exchange and noncompliance of parents when it is used to prevent recurrent attacks.

- However, transfusions for priapism have been associated with ASPEN syndrome, a syndrome characterized by the association of SCD, priapism, exchange transfusion, and neurologic events. The most serious event associated with this syndrome is cerebrovascular accident.
- Exchange blood transfusion:
    - This is done using packed RBCs.
    - This however may be associated with neurological complications including headaches, seizures and obtundation.
    - These complications may be related to the rapid elevation of Hb to above 12 g/dl and release of procoagulant and vasoactive factors from the corpora cavernosa.
    - To ovoid this, the target of exchange RBCs transfusion should be a Hb <10 g/dl and hemoglobin S <50 %.
    - A regular simple packed RBCs transfusion was found beneficial for those with stuttering or repeated attacks of priapism. The aim is to reduce HbS level to less than 30 %.
- Other therapies reported in the literature include calcium-channel blockers, such as verapamil, diltiazem, and nifedipine; hyaluronidase; and anticoagulants.

23.9.8 Complications of Priapism and Prognosis

- Most episodes of priapism resolve without complications.
- These are usually of short duration.
- Prolonged episodes of priapism on the other hand may lead to fibrotic changes in the corpora cavernosa and subsequently erectile dysfunction.
- These changes are time dependent and after 24–48 h of priapism irreversible changes develop leading to erectile dysfunction.
- It has been reported that SCA patients who present with priapism and seek medical advice within 12 h usually retain normal erectile function while all those who present beyond 36 h after the onset of priapism develop erectile dysfunction.
- If irreversible damage has been done, long-term management of erectile dysfunction may be treated with placement of a penile prosthesis to restore function depending on the preference of the patient.
- A severe and prolonged episode of priapism will result in cavernous smooth muscle necrosis, fibrosis, and ultimately penile shortening.
- If erectile function is unlikely to recover, immediate implantation of a penile prosthesis may, therefore, be considered to avoid the complications of penile fibrosis and shortening of the penis.
- The prognosis for erectile function in sickle cell patients is poor.
- Most authors report that one fourth to one half of patients become impotent after prolonged episodes of priapism.
- The prognosis may be better for prepubertal children.
- Acute cases have a much poorer prognosis than cases of intermittent priapism.

Further Reading

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Undescended Testes (Cryptorchidism)

24

24.1 Introduction

- Cryptorchidism is derived from the Greek *κρυπτός*, *kryptos*, meaning hidden and *ὄρχις*, *orchis*, meaning testicle.
- It is defined as the absence of one or both testes from the scrotum (Fig. 24.1).
- Undescended testis was first described in 1786 by Hunter and has been recognized for centuries.
- The first surgical orchiopexy was attempted in 1820 by Rosenmerkal.
- Annandale in 1877 performed the first successful orchiopexy.
- In 1899, Bevan published the principles of testicular mobilization, separation of the processus vaginalis, and repositioning of the testis into the scrotum.
- It is considered the most common birth defect of the male genitalia.
  - It is estimated that about 3 % of full-term and 30 % of premature infant boys are born with at least one undescended testis.
  - It is also estimated that about 80 % of undescended testes descend by the first year of life and the majority of them descend within the first 3 months of life.
  - This makes the true overall incidence of undescended testes around 1 %.
- About 75–80 % of undescended testes are unilateral.
- Cryptorchidism can affect one or both testes and approximately 10 % of cases are bilateral. For unilateral cases the left testicle is more commonly affected
- In 80–90 % of cases, an undescended testis can be felt in the inguinal canal; in a minority the testis or testes are in the abdomen or nonexistent (truly "hidden").
- It has been estimated that the incidence of undescended testis in premature male newborns is about 30 %.
- The incidence of undescended testes in full-term male newborns is 3–5 %.
- This incidence decreases to 0.8 % at 3 months of age as some of these undescended testes will descend to the scrotum spontaneously.
- In the United States, the prevalence of cryptorchidism ranges from 3.7 % at birth to 1.1 % from age 1 year to adulthood.

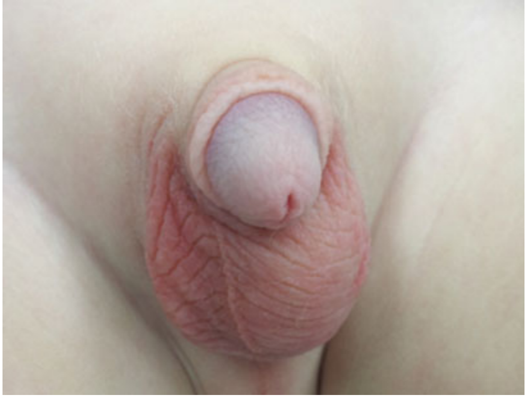

Fig. 24.1 A clinical photograph showing undescended right testis

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A.H. Al-Salem, *An Illustrated Guide to Pediatric Urology*, DOI 10.1007/978-3-319-44182-5_24

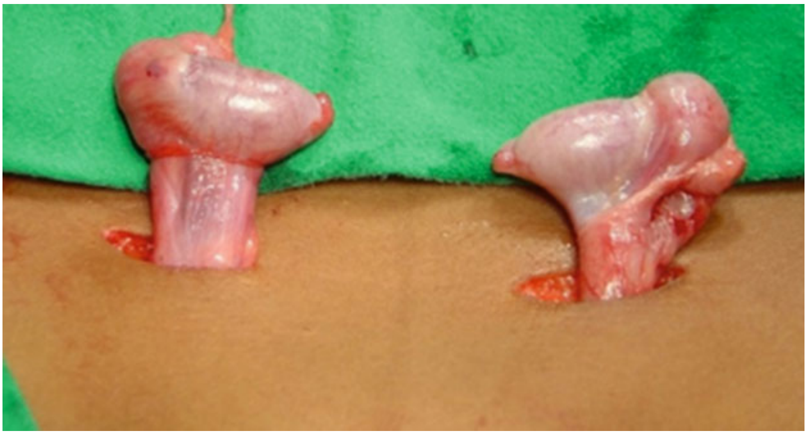


Fig. 24.2 Intraoperative photograph showing bilateral intraabdominal testes in a patient with testicular feminization syndrome

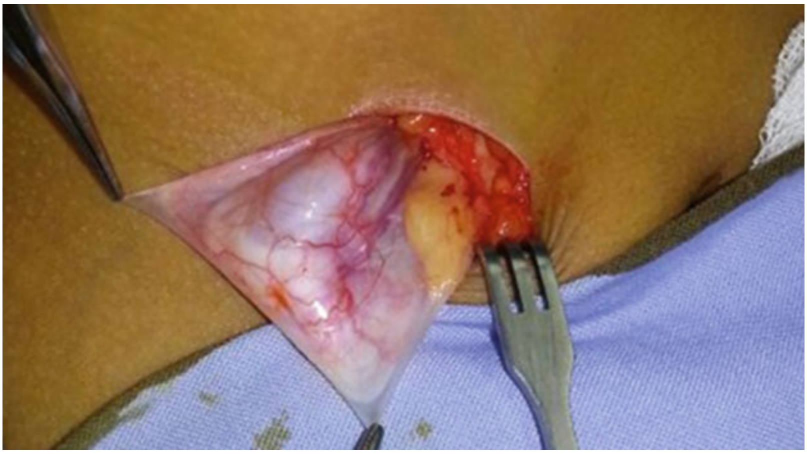


Fig. 24.3 Intraoperative photograph showing a hernia sac containing intraabdominal testis in a patient with testicular feminization syndrome

- Internationally, the prevalence of cryptorchidism ranges from:
  - 4.3–4.9 % at birth
  - 1–1.5 % at age 3 months
  - 0.8–2.5 % at age 9 months
- Siblings of boys with undescended testes are at increased risk for cryptorchidism, with a reported incidence of up to 10 %.
- Cryptorchidism is identified in 1.5–4 % of fathers and 6.2 % of brothers of patients with cryptorchidism.
- Heritability in first-degree male relatives is estimated to be 0.67.
- True undescended testicles rarely descend into the scrotum spontaneously after 4 months of age.
- Factors that Predispose to cryptorchidism include:
  - Prematurity
  - Low birth weight
  - Small size for gestational age
  - Twinning
  - Maternal exposure to estrogen during the first trimester
- Sometimes undescended testes are found incidentally during routine herniotomy in patients with testicular feminization syndrome (Figs. 24.2 and 24.3).
- Early diagnosis and management of the undescended testicle are important to preserve fertility and improve early detection of testicular malignancy.
- The recent improvements in surgical technique, including laparoscopic diagnosis and treatment of undescended testes are likely to improve outcomes.
- According to the guidelines published by the American Urological Association in May 2014:
  - Imaging for cryptorchidism is not recommended prior to referral, which should occur by 6 months of age.

  - Orchiopexy is the most successful therapy to relocate the testis into the scrotum.
  - Hormonal therapy is not recommended.
  - Successful scrotal repositioning of the testis may reduce but does not prevent the potential long-term issues of infertility and testis cancer
  - Appropriate counseling and follow-up of the patient are essential
- Undescended testes are known to be associated with complications which include:
  - Reduced fertility
  - Increased risk of testicular germ cell tumors
  - Undescended testes are known to be associated with inguinal hernia which can be complicated by irreducibility and strangulation
  - Psychological problems when the boy grows up
  - Undescended testes are also more susceptible to testicular torsion and subsequent infarction
  - Undescended testes are more prone to trauma
- It has been shown that men who have had an undescended testis have:
  - Lower sperm counts
  - Poorer quality of sperms
  - Lower fertility rates than normal men
- The likelihood of subfertility increases in those with bilateral undescended testes and increasing age at the time of orchidopexy.
- The risk of subfertility can be reduced by early orchidopexy.
- This is one reason why orchidopexy should be done early as early as 6 months of age and not later than 2 years of age.
- An increased incidence of epididymal abnormalities in undescended testes also contributes to infertility.
- It has been well documented that men with a history of undescended testicle have a higher-than-expected incidence of testicular germ cell cancers. The incidence of testicular cancer among men with an undescended testis is approximately 1 in 1,000 to 1 in 2,500. This is significantly higher than the risk among the general population (1:100,000).
- Orchidopexy does not reduce the risk of testicular cancer, but it makes it easier to diagnose it early through testicular self-examination.
- About 20 % of testicular tumors in men with unilateral cryptorchidism occur on the side with the normally descended testicle.
- Undescended testes have also an increased risk of testicular torsion. Torsion of an intra-abdominal testis may present as an acute abdomen.
- Undescended testes are also known to be associated with an inguinal hernia (Patent processus vaginalis) which is repaired at the time of orchidopexy. If an overt hernia is present in association with undescended testis, hernia repair with orchidopexy should be done at the time of diagnosis. This is to avoid the risk of irreducibility and strangulation.
- The classification of undescended is based on the physical and operative findings of undescended testes:
  - True undescended testicles: This can be
    - Intra-abdominal (nonpalpable)
    - Peeping testis at the internal ring
    - Canalicular or inguinal testes
    - Undescended testes at the upper scrotum
  - Ectopic testicles
  - Retractile testicles
- About one half of nonpalpable testes are found to be intra-abdominal, while the rest represent absent (vanishing) or atrophic testes.
- The vanishing testicle is thought to be caused by intrauterine testicular torsion.
- Sometimes tissue in the scrotum may be palpable and it feels like an atrophic testis. This should not be taken for granted and sometimes this tissue represents the gubernaculum or a dissociated epididymis and vas deferens, and may coexist with an intra-abdominal testis.
- The presence of bilateral nonpalpable testes in a phenotypically male newborn should be taken seriously. The possibility of a genetic female with congenital adrenal hyperplasia and in an older child testicular absence must be kept in mind. These patients should be evaluated including:
  - Pelvic ultrasound
  - Karyotyping

  - Measurements of serum electrolytes, testosterone, luteinizing hormone (LH), follicle-stimulating hormone (FSH), müllerian-inhibiting hormone (MIH), and adrenal hormones and metabolites (17-hydroxyprogesterone).
  - A stimulation test using intramuscular human chorionic gonadotropin (hCG) can be done to check for evidence of testosterone production by the gonads.
  - Pelvic ultrasound is useful in infants with bilateral nonpalpable testes not only to look for gonads but also to exclude the presence of a uterus.
  - Ultrasonography, computed tomography or magnetic resonance imaging, are not sensitive or specific enough to detect the majority of intra-abdominal testes and surgical exploration or laparoscopy is required.

24.2 Embryology and Normal Testicular Development and Descent

- Embryologically, the testes develop in the abdomen along the gonadal ridge from the primitive (indifferent) gonad. This is under the influence of several male genes.
- This occurs at about the sixth week of gestation under the influence of the SRY gene.
  - The SRY gene is located on the short arm of the Y-chromosome (Yp11.3). It is responsible for initiating sex differentiation by downstream regulation of sex-determining factors.
  - This involves expression of several genes including WT1, CBX2 (M33), SF1, GATA4/FOG2 is critical to SRY activation.
  - The SOX9 gene, located on 7q24.3-25.1, is essential for early testis development.
- The second step in male sex differentiation involves internal and external genitalia differentiation.
- During the third to fifth months of intrauterine development, the cells in the testes differentiate into testosterone-producing Leydig cells, and anti-Müllerian hormone-producing Sertoli cells. The germ cells become fetal spermatogonia.
  - The developed testes have two types of cells:
    - The Leydig cells
    - The Sertoli cells
  - The Sertoli cells produce the anti-Müllerian hormone (AMH).
  - The Leydig cells produce testosterone.
  - The AMH acts on its receptor in the Müllerian ducts and causes their regression.
  - Testosterone acts in a critical concentration-dependent and time-dependent manner to induce male sexual differentiation.
  - Testosterone acts on the androgen receptor in the Wolffian ducts to induce the formation of:
    - Epididymis
    - Ejaculatory ducts
    - Seminal vesicles.
  - The Leydig cells also produce insulin-like factor 3 (INSL3, relaxin-like factor), which play a role in the descent of testes to the scrotum.
  - Testosterone is also converted to dihydrotestosterone (DHT) under the influence of 5-alpha reductase enzyme, which acts on the androgen receptor of the prostate and external genitalia to cause its masculinization.
  - Binding of Testosterone and DHT to androgen receptors is necessary for androgen effect.
- The testes remain high in the abdomen until the seventh month of gestation, when they start descending from the abdomen through the inguinal canals into their final position in the scrotum.
- It has been proposed that testicular descent from the abdomen into the scrotum occurs in two phases, under control of somewhat different factors.
  - The first phase:
    - This involves descent of the testes from the abdomen to the entrance of the inguinal canal.
    - This phase is under the influence of the anti-Müllerian hormone (AMH).

- The second phase:
    - This involves descent of the testes through the inguinal canal into the scrotum.
    - This phase under the influence of androgens (testosterone).
    - It was shown experimentally that androgens induce the genitofemoral nerve to release calcitonin gene-related peptide (CGRP), which causes rhythmic contractions of the gubernaculum that help facilitates testicular descend into the scrotum.
    - It was also suggested that the testes secret a hormone called descendin which through a paracrine effect help in testicular descent.
    - In many infants with inguinal testes, further descent of the testes into the scrotum occurs in the first 6 months of life. This is attributed to the postnatal surge of gonadotropins and testosterone that normally occurs between the first and fourth months of life.

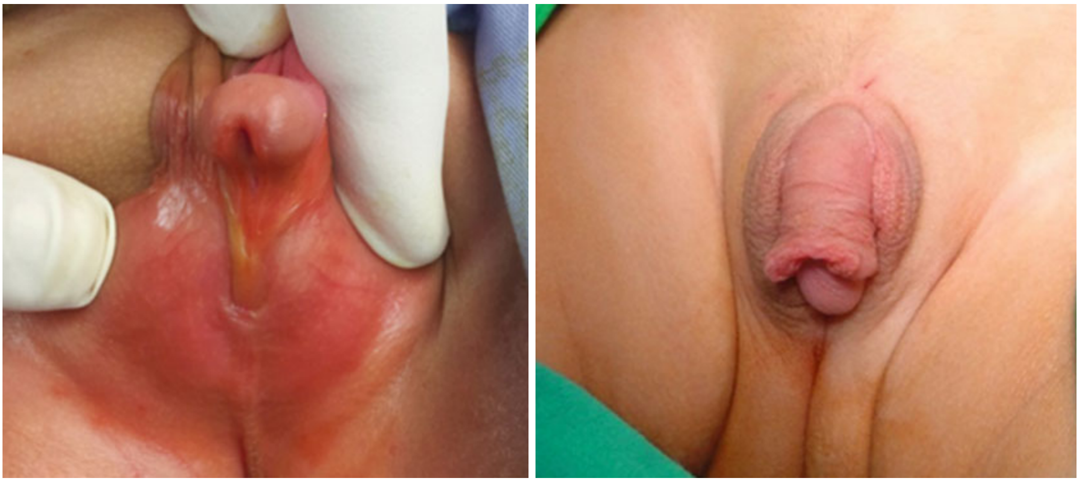
- Factors that can affect testicular descent include:
    - Maldevelopment of the gubernaculum
    - Deficiency or insensitivity to AMH
    - Deficiency or insensitivity to androgen
    - Anatomical factors that interfere with testicular descent
- Spermatogenesis continues after birth.
    - In the third to fifth months of life, some of the fetal spermatogonia residing along the basement membrane become type A spermatogonia.
    - More gradually, other fetal spermatogonia become type B spermatogonia and primary spermatocytes by the fifth year after birth.
    - Spermatogenesis arrests at this stage until puberty.

24.3 Classification of Undescended Testes

- A testis absent from the normal scrotal position can be found any were along the “path of descent” from high in the posterior (retroperitoneal) abdomen, just below the kidney, to the upper part of the scrotum.
    - In the abdomen: These are not palpable
    - In the inguinal canal
    - Just above the scrotum
- Retractile testis: A testis that can easily move between the scrotum and inguinal canal.
- Ectopic testis: A testis that descended but have “wandered” from the normal path of descent to lie outside the inguinal canal.
    - In the superficial inguinal pouch
    - Under the skin of the thigh
    - In the perineum
    - Prepenile are
    - In the opposite scrotum
    - In the femoral canal
- Undeveloped (hypoplastic) testis
- Severely abnormal (dysgenetic) testis
- Vanished testis: This is most likely secondary to intrauterine torsion of testes with infarction and necrosis
- Ascent testis: A testis observed in the scrotum in early infancy can occasionally “reascend” (move back up) into the inguinal canal.
- Most normal-appearing undescended testis are also normal by microscopic examination, but reduced spermatogonia can be found. The tissue in undescended testes becomes more markedly abnormal (“degenerates”) in microscopic appearance between 2 and 4 years after birth. There is some evidence that early orchidopexy reduces this degeneration.

24.4 Causes of Undescended Testes and Risk Factors

- In the majority of undescended testes, no definite cause can be found
- Several factors may contribute to the development of cryptorchidism including genetics, maternal health and other environmental factors. These include:
    - Parents’ exposure to some pesticides
    - Diabetes and obesity in the mother
    - Exposure to regular alcohol consumption during pregnancy
    - Cigarette smoking



Figs. 24.4 and 24.5 Clinical photographs showing two patients with severe hypospadias and bilateral undescended testes

  - Family history of undescended testicle
  - The use of cosmetics by the mother
  - Preeclampsia
  - Prenatal exposure to a chemical called phthalate (DEHP) which is used in the manufacture of plastics
  - Exposure to mild analgesics by pregnant mothers
- Premature infants and low birth weight infants are known to have a higher incidence of undescended testes.
- Intra-abdominal pressure also appears to play a role in testicular descent.
  - Conditions associated with decreased pressure include:
    - Prune belly syndrome
    - Cloacal exstrophy
    - Omphalocele
    - Gastroschisis
  - Each is associated with an increased risk of undescended testes.
- The effect of decreased intra-abdominal pressure is most significant during transinguinal migration to the scrotum, probably in conjunction with androgens and a patent processus vaginalis.
- Epididymal abnormalities often accompany undescended testes, but the causal relationship has not been established.
- Cryptorchidism occurs at a much higher rate in a large number of congenital malformation syndromes including:
  - Down syndrome
  - Prader–Willi syndrome
  - Noonan syndrome
  - Kallmann’s syndrome
  - Laurence-Moon-Biedl syndrome
  - Sever penoscrotal or perineal hypospadias (Figs. 24.4 and 24.5)
  - Prune belly syndrome (Fig. 24.6)
  - Spigelian hernia (Figs. 24.7, 24.8, 24.9, and 24.10)
  - Omphaloceles (Figs. 24.11 and 24.12)
  - Gastroschesis and Cloacal exstrophy (Figs. 24.13 and 24.14)

24.5 Histopathology

- There are several histopathological changes in undescended testes.
- A significant decrease in the number of spermatogonia per tubule (S:T ratio) in undescended testes is seen as early as the second year of life.
- Undescended testes also have atrophic Leydig cells, supporting the observation that testosterone secretion is impaired in cryptorchidism during early infancy.

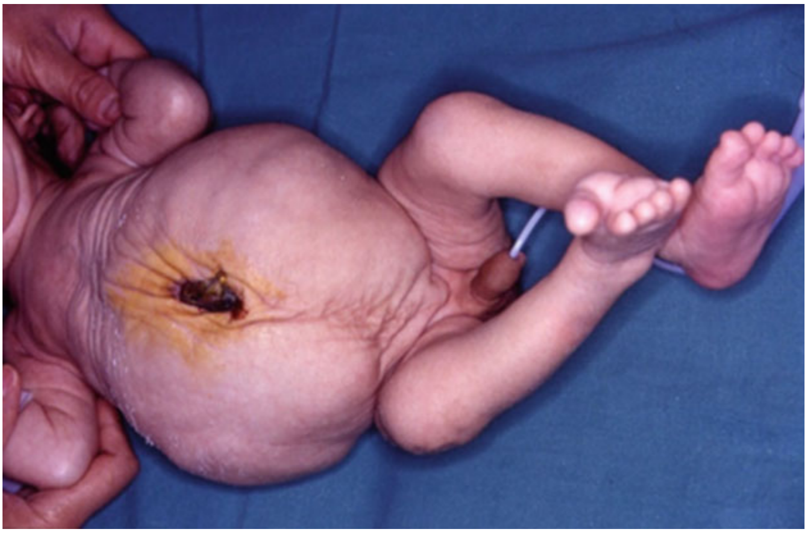
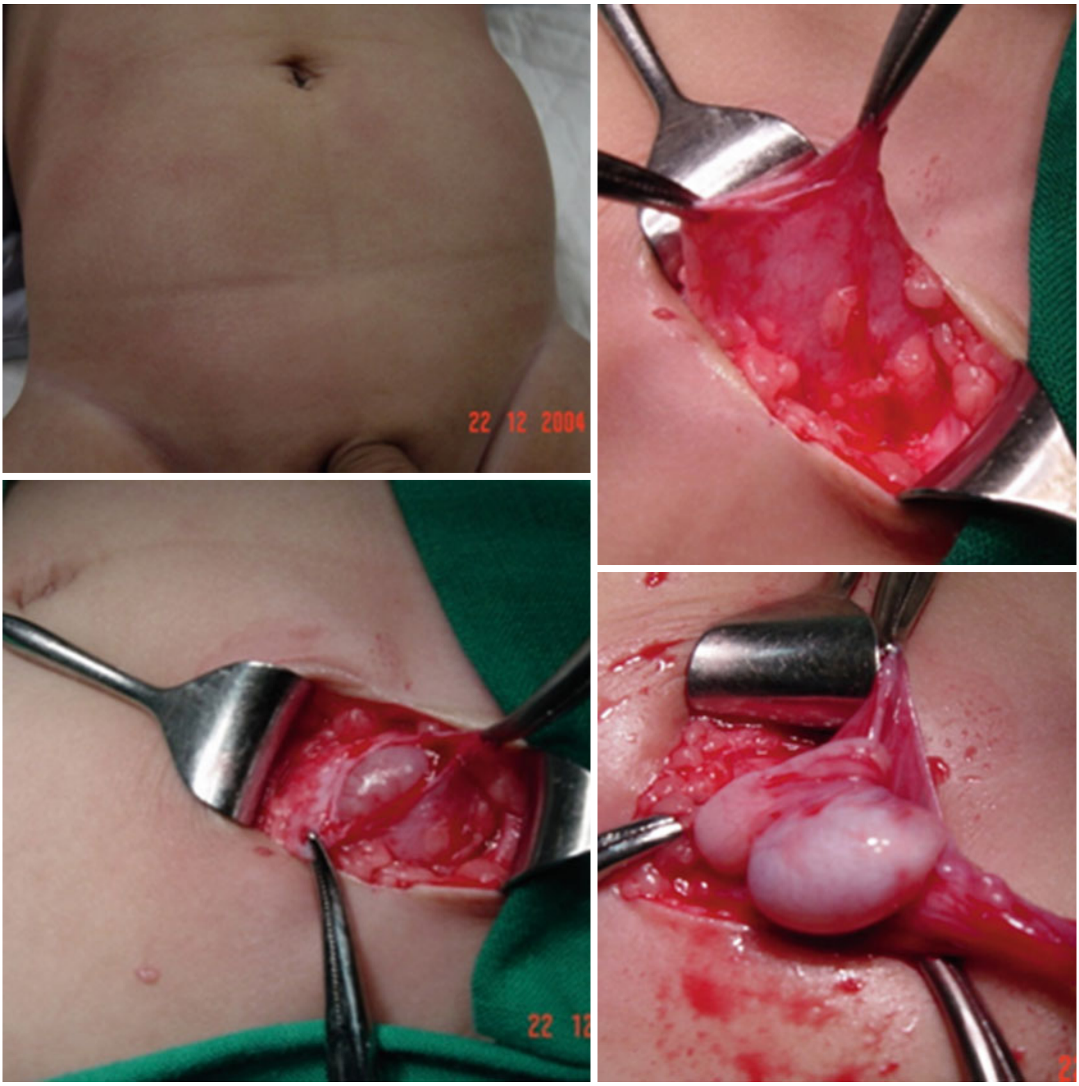


Fig. 24.6 A clinical photograph showing a patient with prune belly syndrome and undescended testes

- Patients with poor testicular histology (S:T ratio less or equal to 0.1) and at high risk for impairment of fertility may benefit from treatment with Buserelin, a luteinizing, hormone-releasing hormone (LHRH) analogue.
- There was a significant increase in mean S:T ratio in testes rebiopsied after orchiopexy and 6 months treatment with Buserelin, while there was no change seen following orchiopexy alone.
- Although the retractile testicle is considered a normal variant, some studies suggest that not all retractile testes have a benign course.
  - Some ascend into the undescended position and these require orchidopexy
  - Others show volume loss and histological abnormalities that are similar but less severe than those found in cryptorchid testes.
  - There are also reports of infertile adults with persistent retractile testicles who have improved sperm counts after scrotal orchiopexy.

24.6 Classification of Abnormal Testes

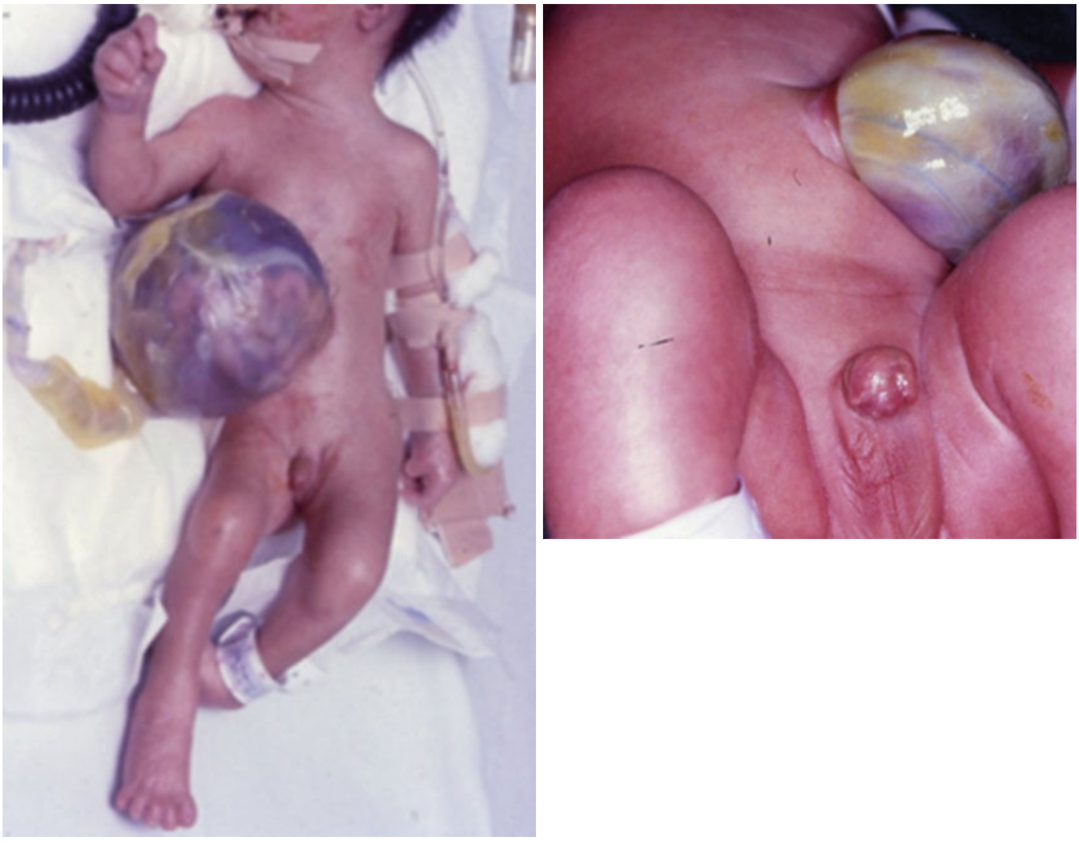
- Normally both testes are present in their normal intra-scrotal position at the time of birth.
- A testis that is absent from the normal intra-scrotal position can be:
  - True undescended testis: The testis can be found anywhere along the "path of testicular descent".
    - High in the posterior (retroperitoneal) abdomen
    - Below the kidney
    - At the inguinal ring
    - In the inguinal canal
    - At the upper scrotum
  - Ectopic testis: This is a testis that "wandered" from the normal path of descent. Ectopic testes exit the external inguinal ring and are then misdirected away from the normal course of descent. This can be found:
    - Outside the inguinal canal
    - Under the skin of the thigh
    - The perineum
    - The opposite scrotum
    - The femoral canal
    - Prepenile
  - Hypoplastic testis
  - Dysgenetic testis
  - Vanished (anorchia) testis
    - The vanishing testicle is thought to be caused by intrauterine testicular torsion.



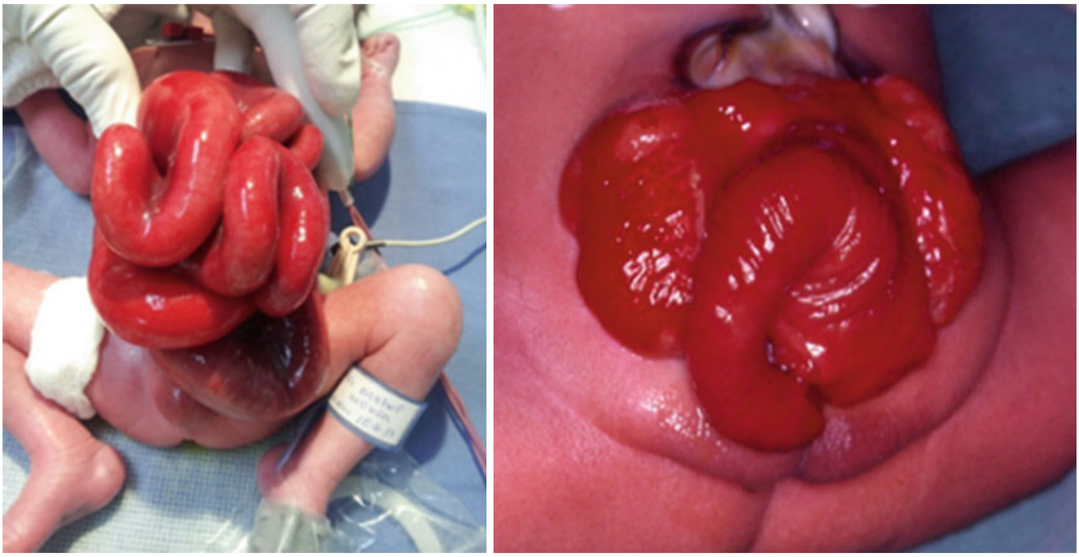
Figs. 24.7, 24.8, 24.9, and 24.10 Clinical and intraoperative photographs showing Spegelian hernia and undescended testis

  - This is most likely during late gestation since most of these testicular remnants are found below the internal inguinal ring.
  - Only 20–40 % of nonpalpable testes are absent upon surgical exploration.
- Ascent testis: A testis that descended normally in the scrotum can occasionally "reascend" back up into the inguinal canal.
- Retractile testis: A testis which can move up and down between the scrotum and inguinal canal. These testes can be manipulated into the scrotum and there is a high risk of ascent.

- About 70–80 % of undescended testis are unilateral.
- 10–20 % of undescended testes are bilateral.
- Approximately 80 % of undescended testes are palpable and 20 % are nonpalpable.
- In 90 % of undescended testes, the testis can be felt in the inguinal canal.
- About one half of nonpalpable testes are found to be intra-abdominal, while the rest represent absent (vanishing) or atrophic testes.

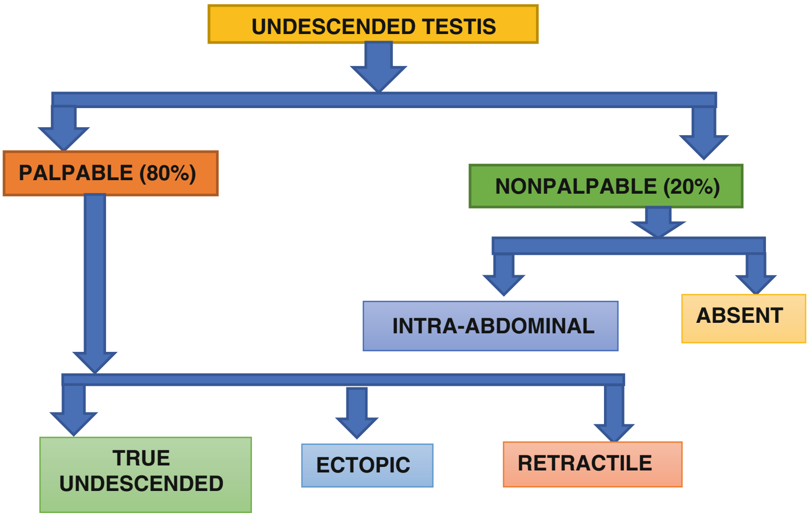


Figs. 24.11 and 24.12 Clinical photographs showing omphaloceles and associated bilateral undescended testes



Figs. 24.13 and 24.14 Clinical photographs of gastroschesis and cloacal exstrophy which are known to be associated with undescended testis

- A patent processus vaginalis is found in more than 90 % of patients with undescended testis
- 30–80 % of undescended testes are associated with some type of epididymal abnormality (Figs. 24.15, 24.16, 24.17, and 24.18).


UNDESCENDED TESTIS
PALPABLE (80%)
NONPALPABLE (20%)
INTRA-ABDOMINAL
ABSENT
TRUE UNDESCENDED
ECTOPIC
RETRACTILE

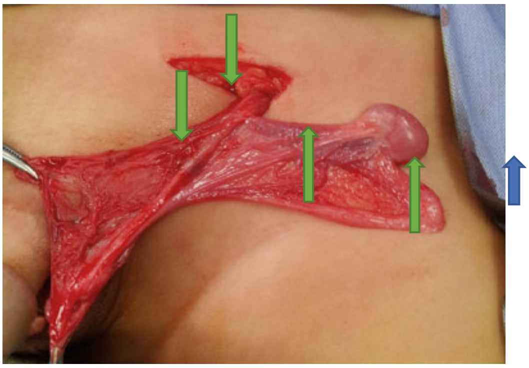


Fig. 24.15 Intraoperative photograph in child with undescended testis. Note the vas looping before it joined the testis. Note also the abnormal epididymis

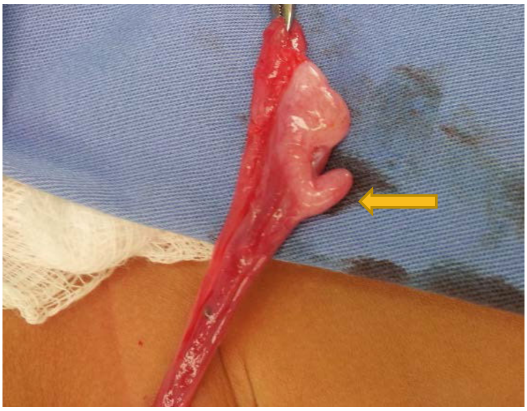


Fig. 24.16 Intraoperative photograph showing undescended testis. Note the abnormal epididymis

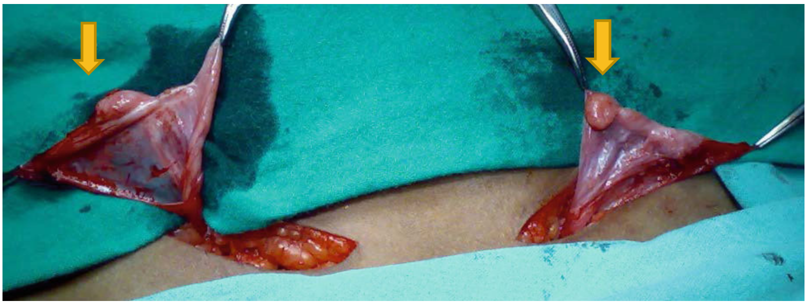


Fig. 24.17 Intraoperative photograph showing bilateral undescended testes which are small in size. Note also the abnormal epididymis

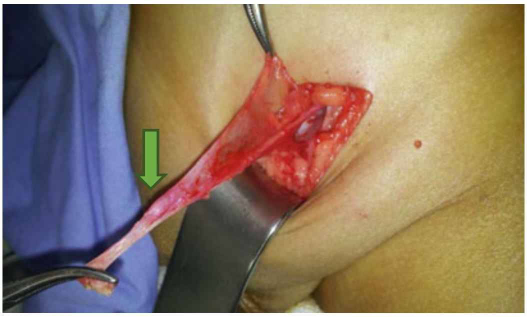


Fig. 24.18 A clinical intraoperative photograph showing a small atrophic testis

24.7 Clinical Features and Diagnosis

- The patient should be warm and relaxed for proper examination.
- The patient can be placed in the frog-leg position for examination. This is especially useful in obese children and makes it easier to palpate the testis.
- The diagnosis of undescended testes is clinical.
- The scrotum is hypoplastic and in those with palpable undescended testes, the testes can be felt in the inguinal canal or upper part of the scrotum.
- In cryptorchidism, the most important factor is whether the testes are palpable or not.
- Approximately 80 % of undescended testes are palpable and 20 % are nonpalpable.
- Nonpalpable testes may be:
  - Intra-abdominal
  - Absent
- Palpable testes may be:
  - Undescended
  - Ectopic
  - Retractile
- Most intra-abdominal testes are found within a few centimeters of the internal ring.
- Absent or vanishing testes are thought to be due to an intrauterine or perinatal vascular event, most likely during late gestation since most of these testicular nubbins are found below the internal inguinal ring.
- Only 20–40 % of nonpalpable testes are absent upon surgical exploration.
- Ectopic testes exit the external inguinal ring and are then misdirected along the normal course of the testis.
- Ectopic testes can be found in the:
  - Superficial inguinal pouch
  - Femoral triangle
  - Prepenile are
  - Perineal area
  - Contralateral hemiscrotum
- Retractile testes:
  - These may be palpated anywhere along the natural course of the testis, although most of them are inguinal.
  - Although not truly undescended, these testes may be suprascrotal secondary to an active cremasteric reflex. This reflex is usually weak in infants and most active in boys aged 5 years.
  - These testes can be manipulated into the scrotum, where they remain without tension.
  - This condition is considered a variant of normal; however, the risk of ascent may approach 50 %.
  - Ascent probably represents an undescended testis that was almost in normal position. The distinction can be difficult, even to an experienced pediatric urologist. Therefore, children with retractile testes should be monitored regularly, at least until puberty.
- The clinical anatomic position of cryptorchid testes are as follows:
  - Nonpalpable (33 %)
  - Palpable above the pubic tubercle (12 %)
  - Palpable at the pubic tubercle (35 %)
  - Palpable in the upper scrotum (15 %)
  - Ectopic testes (5 %)
- The anatomic position of cryptorchid testes at the time of surgery are as follows:
  - Intra-abdominal testis (9 %)
  - Peeping testis (20 %)
  - Palpable at the pubic tubercle (42 %)
  - Palpable at upper scrotum (8 %)
  - Superficial inguinal pouch (SIP)/ectopic – 12 %
  - Absent or atrophic – 9 %

- Associated anomalies:
  - Patent processus vaginalis
  - Abnormal epididymis: Epididymal abnormalities are seen in 32–79 % of children with undescended testis
  - Cerebral palsy
  - Mental retardation
  - Wilms tumor
  - Abdominal wall defects (e.g. gastroschisis, omphalocele, prune belly syndrome)
  - Hypospadias
- It is important to distinguish between a true undescended testis and a retractile one. In retractile testes, the scrotum is usually developed and the testes can be brought down to the bottom of the scrotum. Sometimes, the scrotum is not well developed in those with retractile testes that are outside the scrotum most of the time.
- Retractile testes are more common than truly undescended testes and do not need to be operated on.
- In those with non-palpable testes, pelvic ultrasound or magnetic resonance imaging is performed to locate the testes.
- The presence of a uterus by pelvic ultrasound suggests either persistent Müllerian duct syndrome (AMH deficiency or insensitivity) or a severely virilized genetic female with congenital adrenal hyperplasia.
- A karyotype can confirm or exclude forms of dysgenetic primary hypogonadism, such as Klinefelter syndrome or mixed gonadal dysgenesis.
- Hormone levels (especially gonadotropins and AMH) can help confirm that there are hormonally functional testes.
- An unambiguous micropenis, especially accompanied by hypoglycemia or jaundice, suggests congenital hypopituitarism.

24.8 Treatment

- Benefits of orchidopexy:
  - Increase the likelihood of fertility
    - Infertility is associated with cryptorchidism, and the risk of infertility increases with the degree of maldescent.
    - Moreover, approximately 23–86 % of maldescended testes have been associated with some form of epididymal abnormality. The severity of these epididymal abnormalities is more in those with intra-abdominal testis.
  - Males with undescended testis are 40 times as likely to develop testicular cancer as males without undescended testis.
  - Ten percent of testicular cancer cases involve patients with undescended testis.
    - Recent studies have shown that prepubertal orchiopexy reduces this risk.
    - Clearly, the ability for patients to perform testicular self-examination with the testes in the scrotum is a benefit of surgery.
    - The location of the undescended testis affects the relative risk of testicular cancer. Up to 50 % of malignant testicular tumors associated with cryptorchidism involve intra-abdominal testes.
    - Seminoma is the most common malignant tumor type associated with cryptorchidism.
  - Correction of associated hernia: A patent processus vaginalis is found in more than 90 % of patients with undescended testis.
  - Prevention of testicular torsion
  - Prevention of traumatic injury to the testis against pubic bone
  - Preventing of psychological effects of an empty scrotum
- The timing of orchidopexy is still not well established.
- It was shown that an undescended testes is likely to descend within the first 4–6 months, so an undescended testes that does not descend by this time is unlikely to descend and needs to be operated on.
- The treatment of undescended testes can be:
  - Hormonal
  - Surgical
  - A combination of the two
- Hormonal treatment:
  - This is based on the fact that testicular descent is hormonally mediated and so it can be induced with hormone administration.

- The use of hormonal therapy however is still controversial.
- There are those who advocate using hormonal therapy even for palpable undescended testes. Hormonal therapy is sometimes attempted and occasionally successful.
- Hormonal therapy has been employed in Europe for many years as a primary therapy for cryptorchidism; the main hormones used are human chorionic gonadotropin (hCG) and luteinizing hormone (LH)-releasing hormone (LHRH).
- The most commonly used hormone therapy is human chorionic gonadotropin (HCG).
- hCG, which is administered intramuscularly is the main hormonal treatment for undescended testes.
- There are many protocols for the use of hCG.
  - One such protocol is the administration of 1,500–2,500 U two times per week for 4 weeks.
  - Others use smaller dosage depending on the age of the patient.
    - <1 year old: 500 units are given two times per week for five to ten doses.
    - 1–2 year old: 1,000 units are given two times per week for five to ten doses.
    - >2 year old: 1,500 units are given two times per week for five to ten doses.
- The reported success rates of hCG hormonal therapy is variable ranging from 5 % to as high as 50 %.
- Others use GnRH analogs such as nafarelin or buserelin.
- Gonadotropin-releasing hormone (GnRH) is suggested to be more effective than hCG in achieving testicular descent. This however is not widely used because of conflicting results.
- Many surgeons do not consider the success rates of hormonal therapy high enough to be worth the trouble since the surgery itself is usually simple and uncomplicated.
- Side effects of hCG include:
  - Increased penile size
  - Growth of pubic hair
  - Increase in scrotal rugae
  - Pigmentation
  - Erection
  - Increased testicular size
  - Hyperactivity and aggressive behavior

- Surgical treatment:
  - The treatment of undescended testes is surgical orchidopexy.
  - At present, surgical orchidopexy is to be done at approximately 1 year of age.
  - This recommendation is based on several factors:
    - Spontaneous testicular descent is unlikely after this age
    - Histological abnormalities are subsequently more likely
    - Orchidopexy also allows early detection of any testicular cancer, reduced risk of trauma and torsion, and improvement in germ cell function and ultimate prognosis of fertility
    - Treatment of associated hernia when present
    - Surgical orchidopexy avoids several hormonal injections and their side effects.
  - In those with palpable undescended testes, open orchiopexy (inguinal orchidopexy) is the treatment of choice.
  - Others use a scrotal approach to mobilize and fix palpable undescended testes.
  - This is often performed as an outpatient procedure.
  - Several surgical approaches to the undescended testis have been described.
  - The approach chosen is determined by the position of the testis and the surgeon's expertise.
  - The palpable testis can be approached via one of the following approaches:
    - A scrotal
    - A subinguinal
    - An inguinal (Fig. 24.19)
    - A suprainguinal approach
  - Sometimes exploration may reveal a small atrophic testis with a vas and vessels. This

suggests an intrauterine torsion. The contralateral testis needs to be fixed to prevent subsequent torsion (Fig. 24.20).

- Rarely, exploration for an undescended testis may reveal features of persistent Mullerian duct syndrome (Fig. 24.21).
- The nonpalpable testis can be approached via one of the following approaches:
  - An inguinal
  - A suprainguinal
  - A laparoscopic
- In patients with intraabdominal undescended testis, laparoscopic assisted orchidopexy is performed.
- Diagnostic laparoscopy is the most reliable technique for localizing the nonpalpable testis.
- It is performed in conjunction with definitive therapy (laparoscopic orchiopexy or open orchiopexy).
- Laparoscopic findings can be helpful in determining the need for inguinal exploration, for deciding between one-stage and two-stage repair, and for assessing gonadal viability.
- Blind-ending vas and vessels confirm the diagnosis of a vanishing testis and do not warrant further therapy.

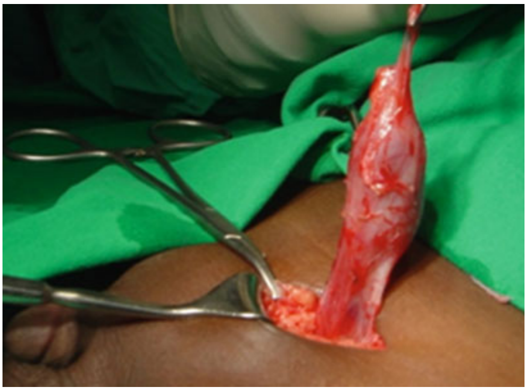


Fig. 24.19 Intraoperative photograph showing an inguinal approach to undescended testis. Note the normal looking testis

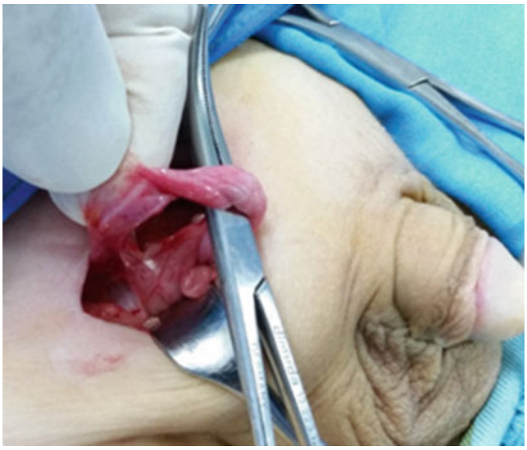


Fig. 24.20 Clinical intraoperative photograph showing a small atrophic testis. Note the intact vas and vessels

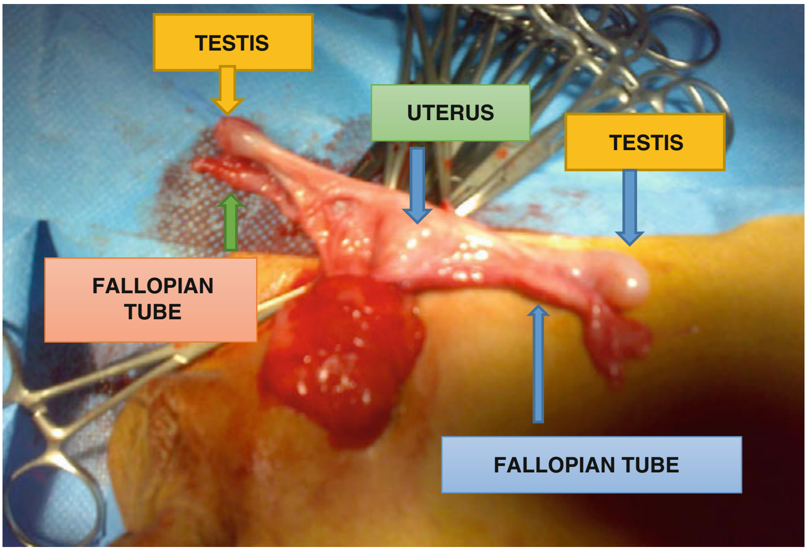


Fig. 24.21 A clinical intraoperative photograph of a patient with bilateral undescended testes. On exploration, he was found to have features of persistent Mullerian duct syndrome with uterus, and fallopian tubes

  - In the presence of blind-ending vas and vessels or a testicular nubbin, the contralateral side should be explored and the testis fixed trans-scrotal to prevent possible testis torsion on the other side.
  - Intra-abdominal blind-ending vas and vessels are found in 10 % of boys with nonpalpable testes.
  - Orchiectomy is advocating for those with small intra-abdominal testis or an abnormal testis.
  - The principal major complication of all types of orchiopexy is loss of the blood supply to the testis, resulting in loss of the testis due to ischemic atrophy or fibrosis.
- Length-increasing maneuvers:
  - The Prentiss maneuver involves rerouting the cord under the epigastric vessels or the division of epigastric vessels.
  - The internal inguinal ring can be opened to perform more complete retroperitoneal mobilization.
  - The Fowler-Stephens principle involves dividing the testicular vessels to allow the blood supply to the vas deferens to keep the undescended testis viable. The testicular vessels should be divided away from the testis.
  - Testicular autotransplantation can be performed by transecting the testicular vessels and by performing a microvascular anastomosis to the inferior epigastric vessels.

24.8.1 Success of Surgical Treatment

- Orchiopexy for palpable testis has a success rate placing the testis in its normal intrascrotal position in the range of 80–90 %.
- The success rate of orchiopexy for nonpalpable testis is variable depending on the technique used as follow:
  - Inguinal approach (60–88 %)
  - Suprainguinal approach (Up to 95 %)
  - One-stage Fowler-Stephens procedure (67–96 %)
  - Two-stage Fowler-Stephens procedure (77–95 %)
  - Microvascular transplantation (83–96 %)
  - Laparoscopic orchiopexy (80–95 %)
  - Laparoscopic Fowler-Stephens procedure (Up to 96 %)

24.9 Complications of Orchidopexy

- Testicular atrophy as a result of ischemic injury during dissection (5 %)
- Failure of orchiopexy (8 % for palpable undescended testes and 25 % for those with intra-abdominal testes)
- Injury to vas deferens (1–2 %)
- Ascent of the testis (<10 %)
- Epididymoorchitis
- Wound infection
- Bleeding and hematoma
- Hydrocele

24.10 Infertility and Undescended Testes

- Men with undescended testes have reduced fertility, even after orchiopexy in infancy.
- The reported infertility rate in those with unilateral undescended testis is of about 10 %, when compared with about 6 % reported in the general population of adult men.
- The reported fertility reduction after orchidopexy for bilateral cryptorchidism is about 38 %, or six times that of the general population.
- To reduce this, early orchidopexy is recommended for these patients.
- It was shown that delayed orchidopexy after the second year of life will lead to degeneration of spermatogenic tissue and reduced spermatogonia counts. There are several factors that contribute to this including exposure of the undescended testes to a higher temperature.
- A factor contributing to infertility in those with cryptorchidism is the high rate of anomalies of the epididymis in these patients.
- Approximately 6 % of infertile men have a history of orchiopexy or untreated cryptorchidism.

- The rate of infertility is higher in patients with bilateral cryptorchidism than in those with unilateral cryptorchidism or in the general male population.
- The paternity rate for patients with bilateral cryptorchidism is around 60 % versus 90 % in patients with unilateral cryptorchidism.
- The paternity rate in those with unilateral cryptorchidism is slightly less than the 94 % in the general population.
- The location of the undescended testis may play a role in fertility potential.
- Worsening testicular biopsy findings are correlated with high locations of undescended testis (e.g. intra-abdominal testis).
- Normal spermatogram findings are found in 20 % of patients with bilateral undescended testis compared with 75 % of patients with unilateral cryptorchidism.
- The rate of germ-cell aplasia substantially increases after age 2 years.
- Semen quality may be impaired in men with a history of unilateral cryptorchidism.
- For men with a history of bilateral cryptorchidism, the prognosis for fertility is worse and this was not shown to improve by type or timing of treatment.

24.11 Undescended Testes and the Risk of Cancer

- It has been estimated that about 1 in 500 men born with unilateral or bilateral undescended testes develop testicular cancer.
- In patients with cryptorchidism, the risk of testicular cancer is 3–5 %, a four to sevenfold greater risk than the 0.3–0.7 % reported in the healthy population.
- The peak incidence of testicular cancer occurs in the third and fourth decades of life.
- The risk of testicular cancer is higher for those with intra-abdominal testes.
- It has been estimated also that a normally descended testis of a man with undescended testis on the other side has about a 20 % higher cancer risk than normal men.
- The risk of malignancy in the undescended testis is four to ten times higher than that in the general population and is approximately 1 in 80 with a unilateral undescended testis and 1 in 40 to 1 in 50 for bilateral undescended testes. The peak age for this tumor is 15–45 year.
- To avoid delay in diagnosis of testicular tumors, it is important to teach boys who had orchidopexy as infants to do testicular self-examination and seek early medical advice when they feel testicular masses.
- This however is not the case for those with intra-abdominal testes where tumors are not recognized before they reach a considerable size or metastasize.
- While orchidopexy may not protect patients from developing testicular malignancy, the procedure allows for earlier detection through self-examination of the testicles.
- A mass developing in a scrotal testis following orchidopexy is far easier to recognize than a mass in an intra-abdominal testis. Orchidopexy makes detection of testicular tumors easier. Orchidopexy however does not lower the risk of developing testicular cancer.
- The most common tumor developing in an undescended testis is a seminoma (65 %); but following orchidopexy, seminomas represent only 30 % of testis tumors.
- The most common tumor in an undescended testis is a seminoma, whereas the most common tumor after successful orchiopexy is non-seminomatous germ-cell tumor.
- Approximately 20 % of these tumors occur in a contralateral descended testis.
- Carcinoma in situ occurs in approximately 0.4 % of patients undergoing orchiopexy.
- Orchiopexy is not protective against subsequent testis cancer but does place the testis in a favorable position for routine self-examination, which is important in the early recognition of testicular cancer. The patient and family must be educated about the risk of future testicular cancer.
- The risk of testicular cancer in men with a history of cryptorchidism:
  - There is a relative risk of 4.7 % in men with a history of cryptorchidism.
  - This is essentially for intra-abdominal testicles, and this risk is not altered by orchiopexy.

- Approximately 15–20 % of tumors also occur in the contralateral descended testis.
- Most tumors occurring in testes after previous successful orchiopexy are commonly non-seminomatous germ cell tumors, while those arising in abdominal testes are most frequently seminomas.

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Varicocele

25

25.1 Introduction

- The testes are supplied by blood vessels that originate in the abdomen and course down through the inguinal canal as part of the spermatic cord to the testis.
- The testis is drained by a plexus of veins called the pampiniform venous plexus. These course upward and coalescence to form the testicular vein. The left testicular vein drains at right angle into the left renal vein while the right testicular vein drains directly into the inferior vena cava.
- Upward flow of blood in the veins is ensured by small one-way valves that prevent backflow.
- A varicocele is an abnormal enlargement and tortuosity of the pampiniform plexus of veins (Fig. 25.1).
- Varicoceles result from defective valves, or compression of the vein by a nearby structure. This leads to dilatation of the testicular veins and the formation of a varicocele.
- The true incidence of adolescent varicoceles is not known because most adolescent varicoceles are asymptomatic.

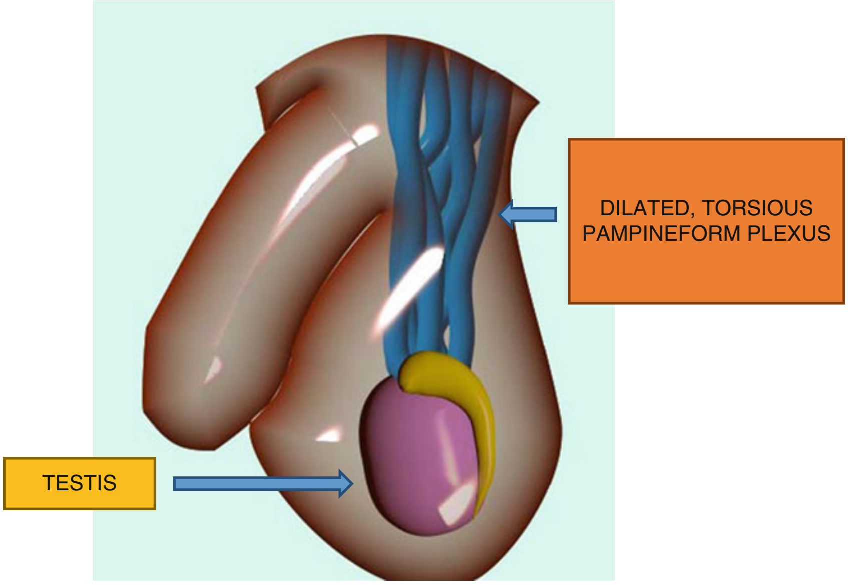

Fig. 25.1 Diagrammatic representation of a varicocele

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A.H. Al-Salem, *An Illustrated Guide to Pediatric Urology*, DOI 10.1007/978-3-319-44182-5_25

- The initial presentation of varicoceles usually occurs during puberty, with an incidence in 13-year-old adolescent boys equal to that of adult men (15 %).
- Rarely, varicoceles are noted in the prepubertal period.
- Although varicoceles may be bilateral, they are usually unilateral and almost always on the left side.
- It has been estimated that 90 % of all varicoceles occur on the left side. This is attributed to the fact that the right testicular vein drain directly into the inferior vena cava while the left testicular vein drains at a right angle into the left renal vein. This predisposes to slower drainage in the left testicular vein.
- A unilateral right-side varicocele raises certain concerns and should prompt an investigation for an underlying obstructive cause such as:
  - A tumor
  - Retroperitoneal fibrosis
  - Thrombosis or occlusion of the inferior vena cava
- These patients should be investigated radiographically including computed tomography (CT).
- Situs inversus is another rare cause of a right-side varicocele which must be kept in mind.

25.2 Etiology

- The exact etiology of varicoceles is unknown and various theories have been proposed to explain this taking in consideration the fact that 90 % of all varicoceles occur on the left side.
- Varicoceles are divided into two types depending on the etiology.
  - Primary or idiopathic varicocele
  - Secondary varicocele
- Primary or idiopathic varicocele:
  - This is the commonest type.
  - It occurs as a result of defective valves within the veins along the spermatic cord.
  - This results in backflow of blood into the pampiniform plexus and causes its dilatation, tortuosity and increased pressures.
  - The majority of idiopathic varicoceles occur on the left side.
  - This is because the left testicular vein drains into the left renal vein (at a 90-degree angle), while the right testicular vein drains directly into the inferior vena cava.
  - Isolated right sided varicoceles are rare.
  - Increased length of the left testicular vein:
    - The left vein is 8–10 cm longer than the right testicular vein. This may contribute to an increased pressure in the left testicular vein when compared to the right testicular vein.
- Secondary varicocele:
  - This results from compression of the venous drainage of the testicle.
  - This can develop as a result of pelvic or abdominal tumors that causes compression of the veins draining the testes.
  - A unilateral right-sided varicocele that is newly diagnosed in a patient older than 40 years of age should raise the possibility of an underlying malignancy.
  - The most common cause is renal cell carcinoma (hypernephroma) followed by retroperitoneal fibrosis or adhesions.
  - In the pediatric age group, left-sided Wilms' tumor with extension into the renal vein can cause obstruction of the testicular vein leading to left varicocele. In those with right-sided Wilms' tumor, a varicocele can develop if the tumor extends into the inferior vena cava and leads to obstruction of the right renal vein.
  - "The Nutcracker syndrome":
    - This is one non-malignant causes of a secondary varicocele.
    - In this condition, the superior mesenteric artery compresses the left renal vein between it and the aorta, causing increased pressures which is transmitted retrograde into the left pampiniform plexus of veins.

25.3 Pathophysiology

- The pampiniform plexus of veins is the network of veins that normally drain the testicle.
- Normally, the size of the veins that make up the pampiniform plexus range from 0.5 to 1.5 mm

- This plexus of veins travels along the posterior portion of the testicle with the epididymis and vas deferens, and then into the spermatic cord and upwards where they coalesces to form the testicular vein.
- Upward flow of blood in the veins is ensured by small one-way valves that prevent backflow.
- The right testicular vein drains into the inferior vena cava, while the left testicular vein drains into the left renal vein at right angle to the renal vein, which then drains into the inferior vena cava.
- The pampiniform plexus of veins not only drains the blood from the testes, vas and epididymis but also has an important function to lower the temperature of the testes.
- A varicocele develops when there is dilatation and tortuosity of the veins of the pampiniform plexus.
- It has been estimated that a varicocele develops when the size of these veins exceeds 2 mm.
- The development of a varicocele with these dilated veins leads to an increase in the temperature around the testes resulting in testicular atrophy, reduction in the quality and the quantity of the sperms and infertility. This effect on sperm quantity and quality is progressive.
- It has been shown also that blood from the testes that cannot drain via the pampiniform plexus may drain via communicating vessels through the prostate. The increased flow of blood to the prostate can lead to congestion and enlargement of the prostate gland secondary to cell proliferation resulting from the high concentration of free testosterone reaching directly from the testes to the prostate.
- It has been shown that a varicocele that persists will lead to histopathological changes in the testis which include:
  - The affected testis is abnormally small as compared with the contralateral testis.
  - Seminiferous tubule sclerosis
  - Small vessel degenerative changes
  - Abnormalities of Leydig, Sertoli, and germ cells
  - The subsequent effects of a varicocele on semen include:
    - Decreased sperm motility
    - Lower total sperm counts
    - Increased number of abnormal sperm forms
- These changes may be reversed with corrective surgery.
- The reasons for altered sperm production, testicular size, and morphologic changes in the testis are not clearly understood. The proposed pathophysiologic mechanisms include the followings:
  - The dilated veins in the pampiniform plexus with pooling of venous blood results in increased scrotal and testicular temperature.
  - The increase in testicular temperature will lead to morphologic changes in sperm and testicular tissue.
  - It is suggested that the renal and adrenal metabolites that reflux into dilated spermatic veins affect testicular tissue leading impaired spermatogenesis and compromised testicular hormone production and function.
  - The low oxygen tension in the dilated veins of the testis may result in local tissue hypoxia which could also affect both testicular function and sperm production.
  - As a result of this, there will be a paracrine imbalances in the testicle which may lead to impaired testicular function.

25.4 Grading of Varicoceles

- Dubin and Amelar graded varicoceles into four grades based on physical examination findings as follows:
  - Grade 0:
    - This is a subclinical varicocele which cannot be detected during physical examination and diagnosed with ultrasonography or venography
  - Grade 1:
    - This is detected clinically with difficulty (<1 cm) and increases in size with Valsalva maneuver

- Grade 2:
    - This is easily detected without Valsalva maneuver (1–2 cm)
- Grade 3:

  This a large varicocele that is palpable and can be seen from a distance (>2 cm)
- The degree of testicular atrophy correlates with the varicocele grade.
- No patients with grade 1 varicoceles were noted to have testicular atrophy while 80 % with grade 3 and 30 % with grade 2 varicoceles have testicular atrophy.

25.5 Clinical Features

- Varicoceles are most frequently diagnosed when a patient is 13–30 years of age, and rarely develop after the age of 40.
- They are reported to occur in 15–20 % of all males.
- The prevalence of varicoceles in individuals aged 10–19 years is reported to be approximately 15 % and is similar to the prevalence reported for adults.
- Varicoceles are extremely rare in patients younger than 9 years (Fig. 25.2)
- The vast majority of varicoceles are asymptomatic.
- Varicoceles mat present with:
    - Testicular pain
    - A scrotal mass
    - Acute or chronic scrotal discomfort
    - Visible or palpable enlarged vein
    - Dragging-like or aching pain within scrotum
    - Feeling of heaviness in the testicle
    - Atrophy of the testicle
- There may be a difference in testicular sizes without a palpable varicocele.
- Varicoceles may present as an incidental finding on scrotal ultrasonography done for other reasons.
- Varicoceles are considered as one of the leading causes of adult male infertility and are detected in 35 % of adult males with primary infertility.

25.6 Diagnosis

- The diagnosis of a varicocele is made clinically.
- This is made by carefully palpating the scrotum while the patient is standing.
- Sometimes, the distended veins can be seen on the lateral aspect of the scrotum.
- A small varicocele may feel like a thickened spermatic cord.
- A larger varicocele feels like a bag of worms.
- A varicocele is a non-tender mass.
- When the patient is asked to perform a Valsalva maneuver, the veins of the pampiniform plexus becomes more distended and accentuates the physical findings.
- When the patient is asked to lie down, gravity may allow the drainage of the pampiniform plexus and thus make the mass smaller and

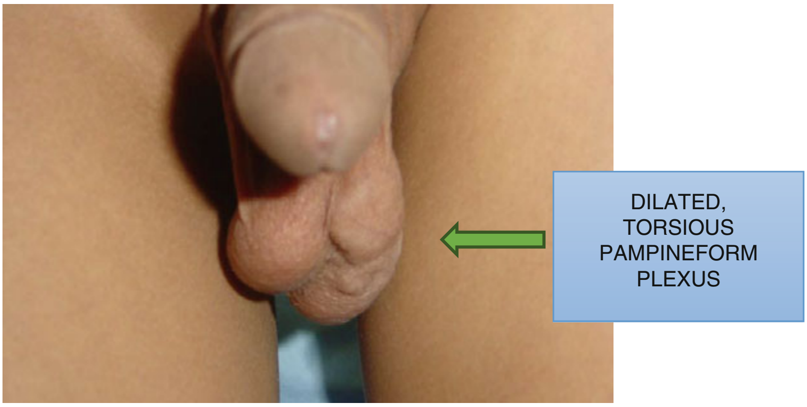

Fig. 25.2 A clinical photograph of a child with left varicocele

not obvious. This is especially true in primary varicocele, and if the varicocele does not become smaller, this is a sign for clinical concern and an obstructive etiology should be considered.

- Both testes should be palpated and the testicle on the side of the varicocele may or may not be smaller when compared to the other side.
- It has been suggested that the testicular size should be assessed with an orchidometer. This is a reliable method of assessing testicular size but ultrasonography is more reliable. A Doppler ultrasound not only demonstrate the varicocele but also can see blood reverse direction in a varicocele with a Valsalva maneuver.
- There are two formulas used to calculate testicular volume based on measurements obtained via ultrasonography:
  - The Lambert formula:
    - Testicular volume = Length × width × depth × 0.71
  - The volume of rotational ellipsoid formula:
    Two variations exist for the volume of rotational ellipsoid formula:
    - Testicular volume = Length × width × depth × 0.52
    - Testicular volume = Length × width^2 × 0.52
  - The average volume of the male testis is 23 ± 3 cm^3.
  - A size difference of more than 3 cm^3 is considered significant.
- Recent studies have shown that varicocele is usually a bilateral disease. The diagnosis of the right side is usually missed clinically and an ultrasonography with a color flow Doppler should be performed to detect a subclinical right varicocele.
- Computed tomography (CT) is rarely indicated but may be useful in those with an isolated right-side varicocele or a secondary obstructive varicocele. This is to exclude a renal or other retroperitoneal mass or thrombosis of the inferior vena cava.
- Venography is rarely used to detect a subclinical varicocele in an infertile adult patient.
- A semen analysis may be done in infertile patients preoperatively as a base line which can be compared to the results postoperatively which are expected to show improvements in semen analysis parameters.

25.7 Treatment

Indications of Treatment

- There are no clear indications for surgical treatment of varicocele in children and adolescents.
- Varicocele associated with testicular growth retardation. These patients are likely to manifest impaired fertility in adulthood.
- Symptomatic painful varicocele.
- A clinically evident varicocele and poor semen quality.
- A palpable varicocele with testicular atrophy and semen abnormality. A 20 % volume deficit in the affected testes is considered an indication for surgical intervention.
- Bilateral varicoceles
- Grade 2 or 3 varicocele

Medical Treatment

- L-carnitine has some beneficial effect on sperm parameters, but it is not as effective as surgery.
- Micronised purified flavonoid fractions (MPFF) (Daflon) have a beneficial effect on reducing varicocele pain and reducing reflux time of left spermatic vein during the Valsalva maneuver.

Embolization Therapy

- An alternative to surgery is embolization.
- This is a minimally invasive treatment that involves passing a small wire through a peripheral vein and into the abdominal veins that drain the testes.
- Embolization materials include balloons, coils, and dextrose.
- Embolization is an effective treatment for recurrent post-surgical varicoceles.

Anatomy

- The spermatic cord extends upward from the testis into the inguinal region, above the scrotum.

- The spermatic cord contains:
  - The spermatic veins
  - The vas deferens
  - The testicular arteries, including the internal spermatic artery (may be multiple branches)
  - The vasal artery
  - The external spermatic artery.
- Above the inguinal region, the vas, with its arterial supply, diverges from the internal spermatic artery and veins, which course through the retroperitoneum, along the psoas muscle.
- A varicocele is situated in the upper scrotum, above the testis.
- The left testicular vein drains into the left renal vein while the right testicular vein drains directly into the inferior vena cava.

Surgical Treatment

- Varicocelectomy (Surgical ligation of the spermatic veins) is the procedure of choice to treat varicoceles.
- Several approaches are used, differing primarily in the level at which the vessels are ligated. These include:
  - Abdominal retroperitoneal (Palomo) approach
  - Inguinal (Ivanissevitch) approach
  - Sub inguinal approach
  - Recently, microsurgical techniques and laparoscopic-assisted transperitoneal or retroperitoneal approaches are used.
- With the inguinal and sub inguinal approaches, the testicular artery is generally spared using a microscope. Visualization of the testicular artery can be ascertained using papaverine or lidocaine administration or using a Doppler probe intraoperatively. Lymphatic vessels are also preserved when possible to prevent future hydrocele formation.
- When surgery is performed in the retroperitoneum or transperitoneally, some authors advocate dividing both the testicular artery and the veins to avoid missing any venous branches. Ligation of the internal spermatic artery in this approach does not usually cause testicular atrophy because of the collateral circulation to the testis. This latter technique relies on the vasal artery as the main blood supply to the testis.

25.8 Postoperative Complications

- Surgical treatment of varicocele is known to be associated with postoperative complications. The frequency of these complications is variable depending on the surgical approach used.
- The microscopic-assisted procedures carry the lowest complication rates (<1 %).
- Hydrocele formation is the most common complication of varicocelectomy and most likely results from lymphatic obstruction.
- Percutaneous embolization is very infrequently associated with hydrocele formation but can cause contrast reactions, puncture of the femoral artery, hemorrhage, extravasation, and migration of embolization balloons.
- These complications include:
  - Hematoma
  - Hydrocele
  - Infection
  - Testicular atrophy
  - Injury to the scrotal tissue or structures
  - Recurrence or persistence of the varicocele
  - Injury to the vas deferens
  - Chronic testicular pain
  - Injury to the artery that supplies the testicle
- The frequency of recurrence depends on the approach used.
  - Embolization has an 80–90 % success rate and a recurrence rate of approximately 10–25 %.
  - The microsurgical approach has a varicocele recurrence less than 5 % of cases and less than 1 % hydrocele development.
  - The inguinal, retroperitoneal, and laparoscopic approaches have a 13–16 % recurrence rate and a 7–9 % risk of hydrocele development.

25.9 Prognosis

- Varicocele can be harmless, but in some cases it can cause infertility and testicular pain.
- Surgical treatment of varicocele may improve fertility and there are reports showing improvement in sperm quality following surgery in 57 % of patients.
- Varicocelectomy improves sperm parameters and testicular volume. These improvements include:
  - Total sperm count
  - Sperm motility
  - Sperm density
  - Sperm morphology
  - Reduces sperm DNA damage and seminal oxidative stress

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Testicular Torsion and Torsion of the Testicular or Epididymal Appendage

26

26.1 Introduction

- Acute scrotal pain requires immediate surgical attention to determine the underlying cause and to treat accordingly.
- The diagnosis of acute scrotal pain may not be straightforward and in some patients, immediate surgical exploration may be necessary in order to treat torsion of the testes early to achieve good results.
- Acute scrotal pain and swelling in children and young adults indicates torsion of the testis until proven otherwise.
- In approximately two thirds of patients, history and physical examination are sufficient to make an accurate diagnosis.
- Testicular torsion is a true surgical emergency and must be differentiated from other complaints of testicular pain because a delay in diagnosis and management can lead to loss of the testicle.
- Testicular torsion may interrupt blood flow to the testis and epididymis.
- The degree of testicular torsion is however variable varying from 180 to 720°.
- Testicular torsion accounts for about 26 % of cases of acute scrotum.
- It occurs when the spermatic cord twists leading to testicular ischemia and necrosis as a result of cutting off the testicle's blood supply.
- The most common underlying cause is a congenital malformation known as a "bell-clapper deformity".
- This congenital anomaly is results in the long axis of the testicle becoming oriented transversely rather than cephalocaudal.
- In this malformation, the testis is inadequately affixed to the scrotum allowing it to move freely on its axis which can lead to twisting of the cord and its vessels.
- In the "bell-clapper deformity", the testis hangs within the scrotum and can swing like a bell clapper in a bell, allowing for easy torsion. Males born with the bell clapper deformity have no attachments around either testicle, so that torsion can potentially occur on either side (Fig. 26.1).
- Bilateral testicular torsion, however, is an exceedingly rare event.
- Testicular torsion occurs more commonly in patients who have an inappropriately high attachment of the tunica vaginalis. This allows the testicle to rotate freely on the spermatic cord within the tunica vaginalis (intravaginal testicular torsion).
- The bell clapper deformity is present in approximately 12 % of males; 40 % of them are affected in both testicles.
- It has been estimated that irreversible ischemia and necrosis of the testis begins around six hours after the onset of torsion.

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A.H. Al-Salem, *An Illustrated Guide to Pediatric Urology*, DOI 10.1007/978-3-319-44182-5_26

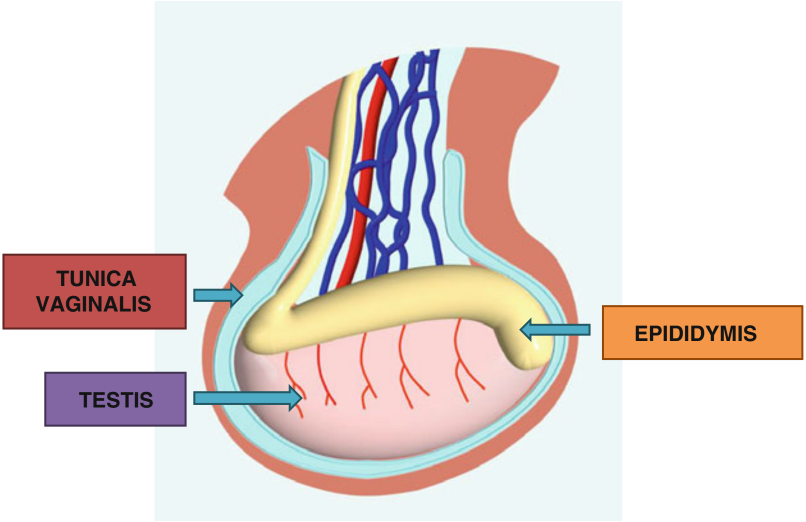


Fig. 26.1 Diagrammatic representation of the bell-clapper deformity. This allows the testicle to rotate freely on the spermatic cord within the tunica vaginalis and predisposes to intravaginal torsion of testis

- This calls for early diagnosis and emergency correction of torsion to minimize the risk of testicular infarction.
- The diagnosis of testicular torsion is clinical and if doubt an emergency Doppler ultrasound can be done.
- Testicular torsion commonly develops during puberty but can also be seen in newborns as a result of intrauterine torsion or soon after birth.
- The exact incidence of testicular torsion is not known but it has been estimated to occur in about 1 in 4,000 to 1 in 25,000 males per year before 25 years of age.
- Testicular torsion is most frequent among adolescents with about 65 % of cases presenting between 12 and 18 years of age.
- It has been estimated that in 95 % of men with testicular torsion the testis can be saved if treated within six hours of the onset of pain.
- Other causes of acute scrotal pain that should be ruled out include:
  - Orchitis
  - Epididymitis, epididymo-orchitis
  - Torsion of the testicular or epididymal appendages
  - Trauma-related causes of acute scrotum
  - Acute hydrocele
  - Testicular tumor
  - Idiopathic scrotal edema

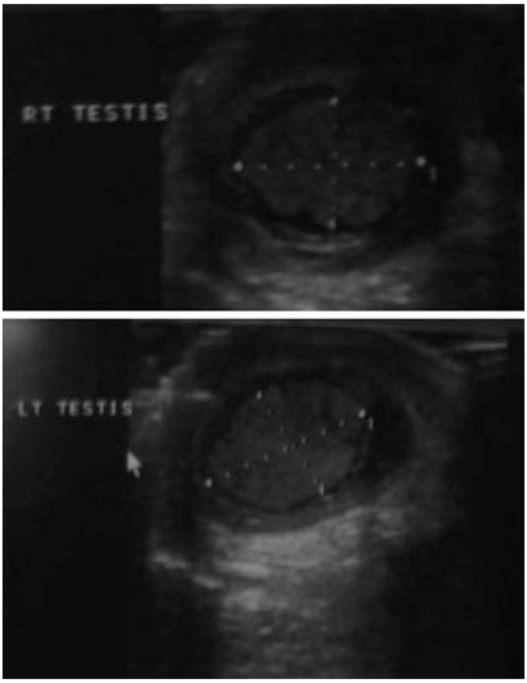
26.2 Etiology and Risk Factors

- The exact etiology of testicular torsion is not known
- The “bell-clapper deformity”
  - This is the commonest cause of testicular torsion
  - It accounts for 90 % of the cases
  - It is a congenital malformation of the processus vaginalis
  - In this condition, rather than the testes attaching posteriorly to the inner lining of the scrotum by the mesorchium, the mesorchium terminates early and the testis is free floating in the tunica vaginalis.
  - This condition is bilateral and calls for fixation of the other testis when one testis is affected. This is to prevent subsequent torsion of the other side.
- A large mesentery between the epididymis and the testis can also predispose itself to torsion, although this is rare.
- Contraction of the spermatic muscles shortens the spermatic cord and may initiate testicular torsion.
- Other etiologic factors involved in intravaginal testicular torsion include:
  - Undescended testicle
  - Sexual arousal or activity
  - Physical exercise

  - An active cremasteric reflex
  - Cold weather.
- A larger testicle either due to normal variation or a tumor increases the risk of torsion.

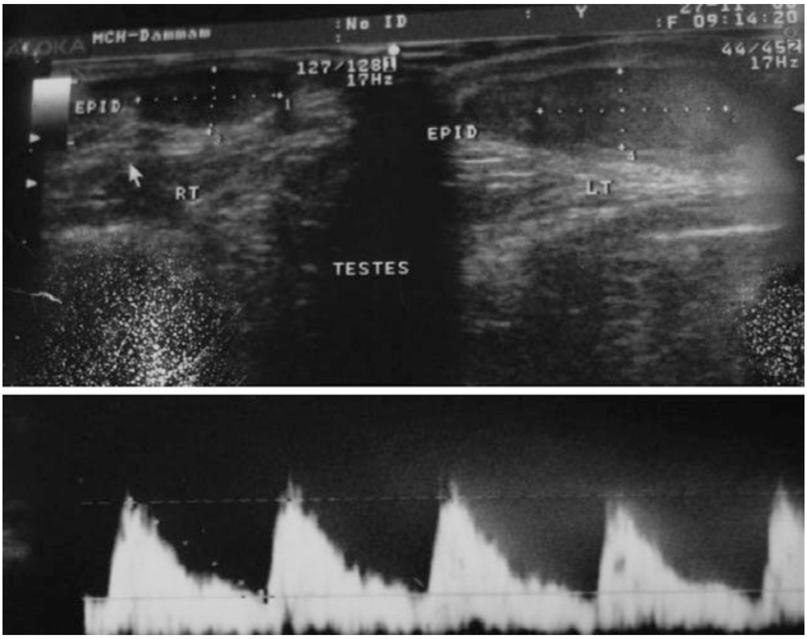
26.3 Diagnosis

- The diagnosis of testicular torsion is clinical based on the history and presenting signs and symptoms.
- With a convincing history and physical examination, no time should be wasted on investigations and immediate surgical exploration should be done.
- Doppler ultrasound should be done only in low suspicion cases to rule out torsion and differentiate this from epididymo-orchitis. Doppler ultrasonography can be used to demonstrate arterial blood flow to the testis while providing information about other testicular pathology. It is about 90 % accurate in diagnosing testicular torsion.
  - In testicular torsion, there is no blood flow or the blood flow is markedly decreased.
  - In epididymo-orchitis, there is normal or slightly increased blood flow.
  - The sensitivity of color Doppler in detecting acute testicular torsion in children is 90–100 %, with specificity being 100 %.
  - Other studies have suggested that color Doppler ultrasonography was only 86 % sensitive, 100 % specific, and 97 % accurate in the diagnosis of testicular torsion (Figs. 26.2 and 26.3).
  - Doppler ultrasonography has (Figs. 26.4 and 26.5):
    - 94 % sensitivity.
    - 96 % specificity.
    - 95.5 % accuracy.
    - 89.4 % positive predictive value.
    - 98 % negative predictive value.



Figs. 26.2 and 26.3 A Doppler ultrasound showing bilateral torsion of testes

- In doubtful cases, an isotope scan (technetium-99 m pertechnetate) can be done. Radionuclide scans have a sensitivity of 90–100 % accuracy in detecting testicular blood flow.
  - This is the most accurate investigation but it is not readily available
  - Add to this the time it requires to organize and do this investigation particularly in cases of torsion where urgency is required
  - In testicular torsion, there is no uptake of the uptake is markedly reduced
  - In epididymo-orchitis, there is normal uptake and uniformly symmetric activity.
  - A urine analysis and culture can be done to roll out infection.
  - The complete blood count can be normal. However, the WBC count is elevated in as many as 60 % of patients who have testicular torsion.
- Surgical exploration should not be delayed for the sake of performing imaging studies.



Figs. 26.4 and 26.5 A Doppler ultrasound showing epididymitis. Note the enlarged left epididymis and the good blood flow to the testis

26.4 Intermittent Testicular Torsion

- This is a less serious variant of testicular torsion.
- It is a chronic condition characterized by the symptoms of testicular torsion but followed by eventual spontaneous detortion and resolution of pain.
- The attack may be associated with nausea or vomiting
- These patients are however at significant risk of developing complete torsion
- It is important recognize this condition and physicians treating these patients should be aware of this.
- The treatment is elective bilateral orchiopexy.
- This is curative and 97 % of patients who undergo bilateral orchidopexy experience complete relief from their symptoms.

26.5 Classification of Testicular Torsion

- Testicular torsion is classified is classified into two types depending on onset:
  - Acute testicular torsion
  - Intermittent testicular torsion
- Testicular torsion is also classified anatomically into two types:
  - Intravaginal torsion
    - This is the commonest type
    - Commonly develops during puberty
    - The torsion occurs within the tunica vaginalis
    - Intravaginal torsion comprises approximately 16 % of patients with torsion presenting in emergency departments with acute scrotum.
    - Thepeak incidence occurs in adolescents aged 13 years.
    - The left testis is more frequently involved.
    - Bilateral cases account for 2 % of all testicular torsions.
  - Extravaginal torsion (Figs. 26.6, 26.7, 26.8, 26.9, and 26.10)
    - This much less common
    - Extravaginal torsion comprises approximately 5 % of all testicular torsions.
    - This type occurs exclusively in newborns
    - The condition is most often a prenatal (in utero testicular torsion) event.
    - It is associated with high birth weight.
    - Up to 20 % of cases are synchronous, and 3 % are asynchronous bilateral.

- This type of torsion occurs outside of the tunica vaginalis, when the testis and gubernaculum can rotate freely.
- The torsion usually occurs intrauterine and rarely soon after birth

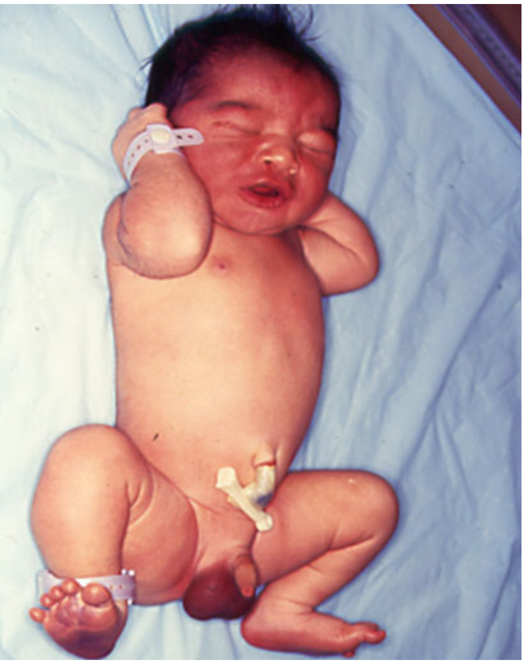
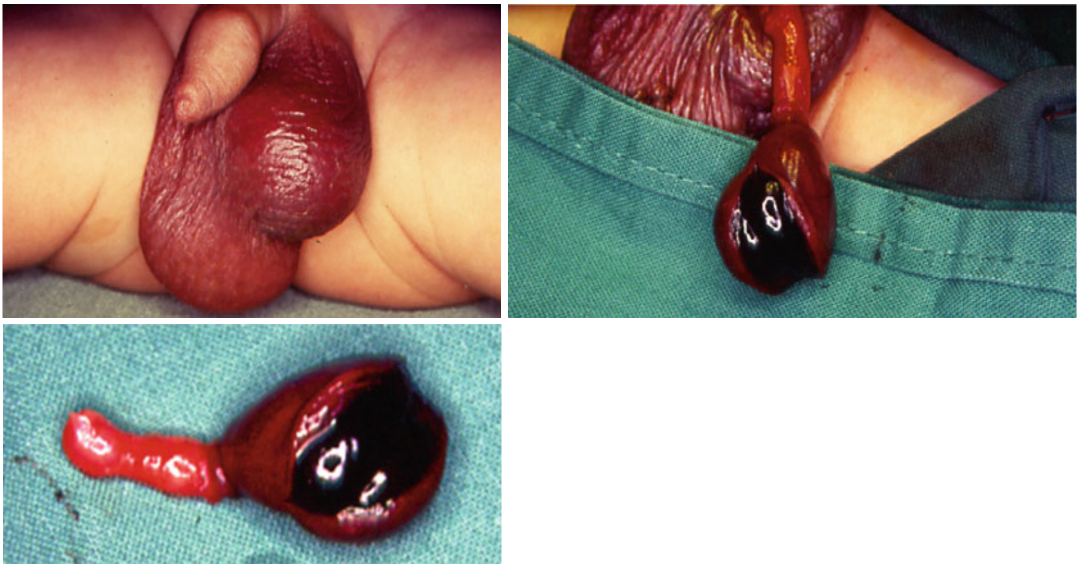


Fig. 26.6 A clinical photograph showing a newborn with intrauterine torsion of testis. Note that the patient is healthy and of good weight

- It is usually unilateral but can also occur bilaterally.
- The newborns with this type of torsion usually present immediately after birth with scrotal swelling, and dark discoloration of the scrotum
- Clinically, the affected testis is usually firm and painless
- The scrotal skin characteristically fixes to the necrotic gonad.
- The affected testis is usually necrotic
- The treatment is orchidectomy and contralateral orchidopexy to obviate the risk of torsion on the other side

26.6 Effects of Testicular Torsion

- Torsion of the testes causes venous occlusion and engorgement as well as arterial obstruction and ischemia and subsequent infarction of the testis. The extent of this depends on two factors:
  - The degree of torsion:
    - Torsion of testis occurs as the testis and the cord rotate between 90° and 180°, compromising blood flow to and from the testis.



Figs. 26.7, 26.8, and 26.9 Clinical and intraoperative photographs showing intrauterine torsion of testes. Note the discoloration of the affected scrotum which is slightly elevated. Note also the frankly necrotic testis

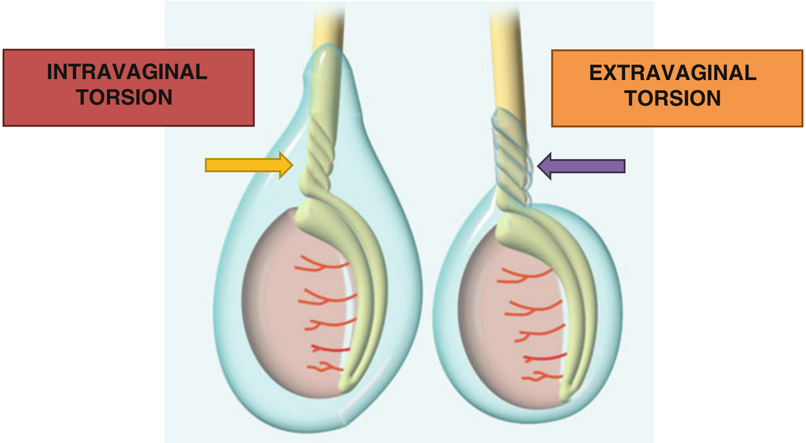


Fig. 26.10 Diagrammatic representation of the two types of testicular torsion, the intravaginal and extravaginal torsions

    - Complete testicular torsion usually occurs when the testis twists 360° or more.
    - Incomplete or partial torsion occurs with lesser degrees of rotation.
    - In some cases, the degree of testicular torsion may extend to 720°.
  - The duration of torsion:
    - The duration of testicular torsion is the most important factor that prominently influences the salvage rates of the affected testis and late testicular atrophy.
    - Testicular salvage is most likely if the duration of torsion is less than 6 h.
    - If 24 h or more elapse, testicular necrosis develops in most patients.

The Duration of Torsion and Testicular Salvage Rate
- <6 h: 90–100 %
- 12–24 h: 20–50 %
- >24 h: 0–10 %

- The decreased fertility observed in patients who developed only unilateral torsion of the spermatic cord, was based on an inherent bilateral testicular abnormalities or an autoimmune mechanism affecting the contralateral testis. This hypothesis however was not supported.

26.7 Clinical Features

- Although testicular torsion can occur at any age, including the prenatal and perinatal periods, it most commonly occurs in adolescent males.
- Testicular torsion is commonly observed in males younger than 30 years, with a peak at 12–18 years.
- The incidence of testicular torsion in males younger than 25 years is approximately 1 in 4,000.
- Testicular torsion more often involves the left testicle.
- Testicular torsion can occur suddenly, with physical activity or may develop during sleep.
- Torsion can occur:
  - Spontaneously
  - During sports or physical activity
  - In relation to trauma in 4–8 % of cases
  - During sleep
- This is an acute emergency and the patient usually present with:
  - The classic presentation of testicular torsion is the sudden onset of severe testicular pain followed by inguinal and/or scrotal swelling.
  - Gradual onset of pain is an uncommon presentation of testicular torsion.
  - The pain may lessen as the necrosis becomes more complete.
  - This may be associated with groin and lower abdominal pain and tenderness

  - In time, a reactive hydrocele, scrotal wall erythema, and ecchymosis become more striking.
  - Scrotal pain that is referred to the lower abdomen may be perceived as not being of scrotal or testicular origin which is one of the causes of delay in seeking early medical advice. Any adolescent boy who complains of lower abdominal pain should also undergo examination of the external genitalia to rule out the possibility of scrotal or testicular pathology.
  - The pain is often associated nausea and vomiting. Approximately one third of patients also have gastrointestinal upset with nausea and vomiting.
  - In the pediatric age group, nausea and vomiting has a positive predictive value of greater than 96 %.
  - Patients rarely report voiding difficulties or painful micturation.
  - In some patients, scrotal trauma or other scrotal disease (including torsion of appendix testis or epididymitis) may precede the occurrence of subsequent testicular torsion.
  - Patients may describe previous episodes of recurrent acute scrotal pain that has resolved spontaneously. This history is highly suggestive of intermittent torsion and detorsion of the testis.
  - Acute testicular torsion developed in 10 % of patients with intermittent torsion while they waited for surgery.
  - Clinically, the affected testis will be swollen, and markedly tender
  - The affected testis lies high up from its normal position usually with an abnormal transverse lie
  - There may be redness of the affected scrotum
  - There may be an associated mild fever
- Physical examination may reveal:
  - A swollen, tender, high-riding testis.
  - Abnormal transverse lie of testis.
  - Loss of the cremasteric reflex.
  - Edema involving the entire scrotum.
  - Enlargement and edema of the testis.
  - Fever is uncommon.
  - Scrotal erythema.
- The cremasteric reflex is almost always absent or diminished on the affected side in patients with testicular torsion. Normally, pinching the inside of the thigh causes the testicles to contract and move up. This reflux may disappear on the affected side
- Prehn's sign: Relief of pain with elevation of the testis. This is a classic physical examination sign but it is not reliable in distinguishing testicular torsion from other causes of acute scrotal pain.
- Although a negative Prehn sign is classically thought to be a predictor of torsion, this is unreliable for diagnosis.
- The most confusing condition with torsion of testis is epididymo-orchitis. In epididymo-orchitis:
  - There is marked redness and swelling of the affected testis
  - The patient is often febrile
  - The cremasteric reflux is usually present
- Epididymitis, orchitis, epididymo-orchitis (Fig. 26.11):
  - These conditions most commonly occur from the reflux of infected urine or from sexually acquired disease caused by gonococci and *Chlamydia.*

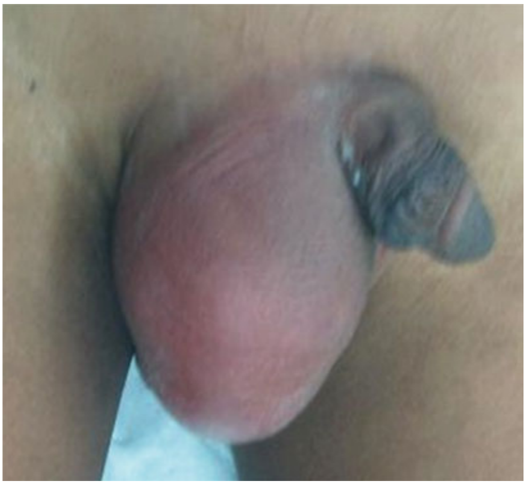


Fig. 26.11 A clinical photograph showing severe epididymo-orchitis with intra-scrotal abscess formation in a child

  - The patients occasionally develop these conditions following excessive straining or lifting and the reflux of urine (chemical epididymitis).
  - These conditions may be secondary to an underlying congenital, acquired, structural, or urologic abnormality and are often accompanied by systemic signs and symptoms associated with urinary tract infection. These include:
    - Pyuria
    - Bacteriuria
    - Leucocytosis
  - A complete urological evaluation (ie, renal sonography, urodynamic study) is necessary in prepubertal boys with acute epididymitis.
- In an acute developing hydrocele:
  - The swelling is usually painless but there may be some discomfort
  - The scrotal contents can be visualized with transillumination
  - Incarcerated hernia if suspected may be diagnosed by careful examination of the inguinal canal
- In idiopathic scrotal edema:
  - In idiopathic scrotal edema, the scrotal skin is thickened, edematous, and often inflamed.
  - The testis is not tender and is of normal size and position.
- Factors predictive of testicular torsion include:
  - Acute onset of pain.
  - Duration of pain of less than 6 h.
  - Fever, nausea and vomiting.
  - History of trauma or activities.
  - Absence of cremasteric reflex.
  - Abnormal transverse direction of testis.

26.8 Treatment

- Testicular torsion is an acute surgical emergency and with early diagnosis and prompt treatment the testicle can often be saved.
- The aim is to restore the blood flow to the affected testis as early as possible.
- It has been estimated that about 40 % of testicular torsion cases result in loss of the testicle.
- The success of salvaging the affected testis is time dependent:
  - If the affected testis is treated either manually or surgically within 6 h, there is a high chance (approx. 90 %) of saving the testicle.
  - If the affected testis is treated at around 12 h from the onset, the success rate of salvaging the testis decreases to 50 %.
  - If the affected testis is treated about 24 h from the onset, the success rate of salvaging the testis drops to 10 %.
  - If the affected testis is treated after 24 h from the onset, the ability to save the testicle approaches 0.
- Typically when testicular torsion occur, the testis rotates towards the midline of the body.
- Non-surgical correction of testicular torsion (manual detorsion):
  - This can sometimes be accomplished by manually rotating the testicle in the opposite direction (i.e., outward, towards the thigh). Rotate the testis in medial to lateral direction.
  - This maneuver can be attempted while waiting for proper surgical exploration but no further time should be wasted.
  - This is usually difficult because of acute pain during manipulation.
  - The procedure for manual detorsion of the testis is similar to the “opening of a book” when the physician is standing at the patient’s feet.
  - Most torsions twist inward and toward the midline (anti-clock wise rotation); thus, manual detorsion of the testicle involves twisting outward and laterally (anti-clock wise).
  - Torsion closes the book and manual detorsion opens the book.
  - Lateral rotation has been described in up to a third of testicular torsions, however, and in such cases further lateral rotation will worsen the condition.

- For manual detorsion in a suspected torsion of the right testicle, the physician is positioned in front of the standing or supine patient and holds the patient's right testicle with the left thumb and forefinger. The physician then rotates the right testicle outward 180° in a medial-to-lateral direction.
- For the patient's left testicle torsion, the physician uses the right thumb and forefinger and rotates the patient's left testicle in an outward direction 180° from medial to lateral.
- Rotation of the testicle may need to be repeated two to three times for complete detorsion.
- Pain relief serves as a guide to successful detorsion, but restoration of blood flow using Doppler ultrasound must be confirmed following the maneuver.
- Other signs suggestive of successful manual detorsion include:
  - Resolution of the transverse lie of the testis to a longitudinal orientation
  - Lower position of the testis in the scrotum
  - Return of normal arterial pulsations detected with a Doppler ultrasound
- Manual detorsion of the affected testicle is not recommended if the duration of torsion is longer than 6 h.
- Following successful manual detorsion, elective bilateral orchidopexy is recommended, to prevent recurrent torsion and protect the contralateral side from torsion.
- The success rate of manual detorsion is variable ranging from 26.5 % to more than 80 %.
- It must be remembered that nonoperative manual detorsion is not a substitute for surgical exploration.
- If manual detorsion is successful (confirmed by color Doppler ultrasound in a patient with complete resolution of symptoms), the patient should undergo definitive surgical fixation of the testes before leaving the hospital, so that the operation can be performed as an urgent rather than emergency procedure.
- A bilateral scrotal orchidopexy is often recommended to treat the torsed testis and prevent torsion of the other testis.

- The treatment of testicular torsion is emergency surgical exploration (surgical detorsion).
  - This done through a scrotal approach.
  - If the testis is found viable, it should be fixed (orchidopexy) and contralateral orchidopexy should be done at the same time.
  - If the testis is found necrotic, orchidectomy should be done and contralateral orchidopexy is done at the same time.
- Patients requiring an orchiectomy because of a nonviable testis may benefit from the placement of a testicular prosthesis.
  - Delay performing this procedure, usually for 6 months, until healing is complete and inflammatory changes resolve.
  - Perform the prosthetic placement through an inguinal incision.
- Recent studies show that exocrine and endocrine function is subnormal in men with a history of unilateral torsion.
- This is based on the following three theories which explain the contralateral disease noted in patients with testicular torsion:
  - Unrecognized repeated injury to both testes
  - Preexisting pathologic condition predisposing to both abnormal spermatogenesis and torsion of the spermatic cord
  - Induction of pathologic changes in the contralateral testis by retention of the injured testis (autoimmune)
  - To explain the decreased fertility observed in unilateral torsion of the spermatic cord, several theories suggest an autoimmune mechanism. This hypothesis is based upon the following:
    - Knowledge of the blood-testis barrier, which isolates the luminal compartment of the seminiferous tubule
    - Inducing experimental allergic orchitis
    - The contralateral testicular disease resembles sympathetic ophthalmia, a cell-mediated immune response

- The placement of a testicular prosthesis is usually delayed for 6 months, until healing is complete and inflammatory changes resolve.

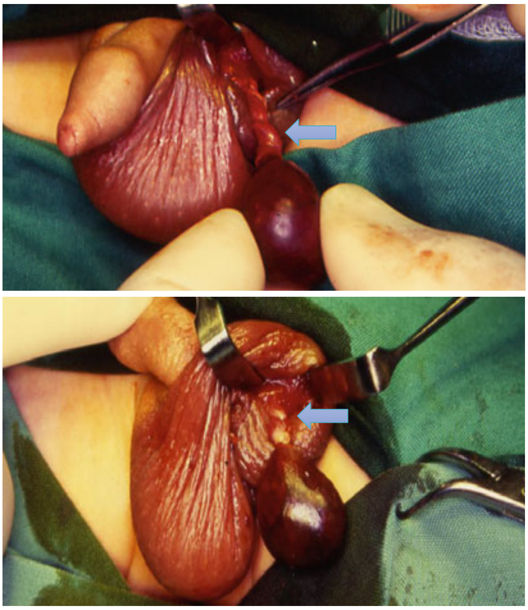
26.9 Intra-uterine Torsion of Testes

26.9.1 Introduction

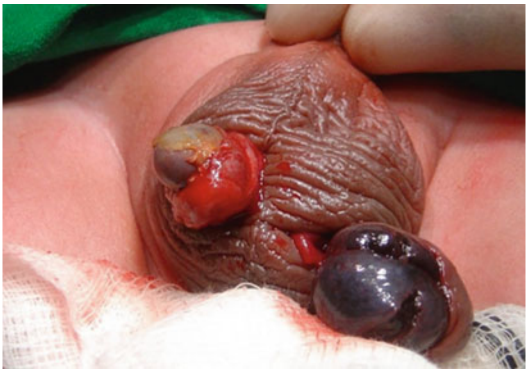
- Intra-uterine torsion of testes is an extravaginal torsion (Figs. 26.12, 26.13, and 26.14).
- It is very rare and seen most commonly in neonates.
- It constitutes approximately 5 % of all testicular torsions.
- The majority of extravaginal torsions occur prenatally (70 %) and 30 % occur postnatally.
- The timing of post-natal torsion is variable. There are cases seen immediately after birth but the majority of post-natal torsions occur within the first 2 weeks.
- Extravaginal torsion is known to be associated with high birth weight.
- Bilateral perinatal torsion is thought to be rare, but an increase in the number of case reports has been observed.

26.9.2 Etiology of Extravaginal Torsion

- The exact etiology of intrauterine testicular torsion is not known
- It is proposed that intrauterine testicular torsion occurs because the tunica vaginalis is not yet secured to the gubernaculum and, therefore, the spermatic cord, as well as the tunica vaginalis, undergo torsion as a unit.
- In neonates, the testes frequently has not yet fully descended into the scrotum, where it becomes attached within the tunica vaginalis. This mobility of the testicle predisposes it to extravaginal torsion.
- Extravaginal torsion is not like the commonly seen intravaginal torsion is not associated with the bell clapper deformity.



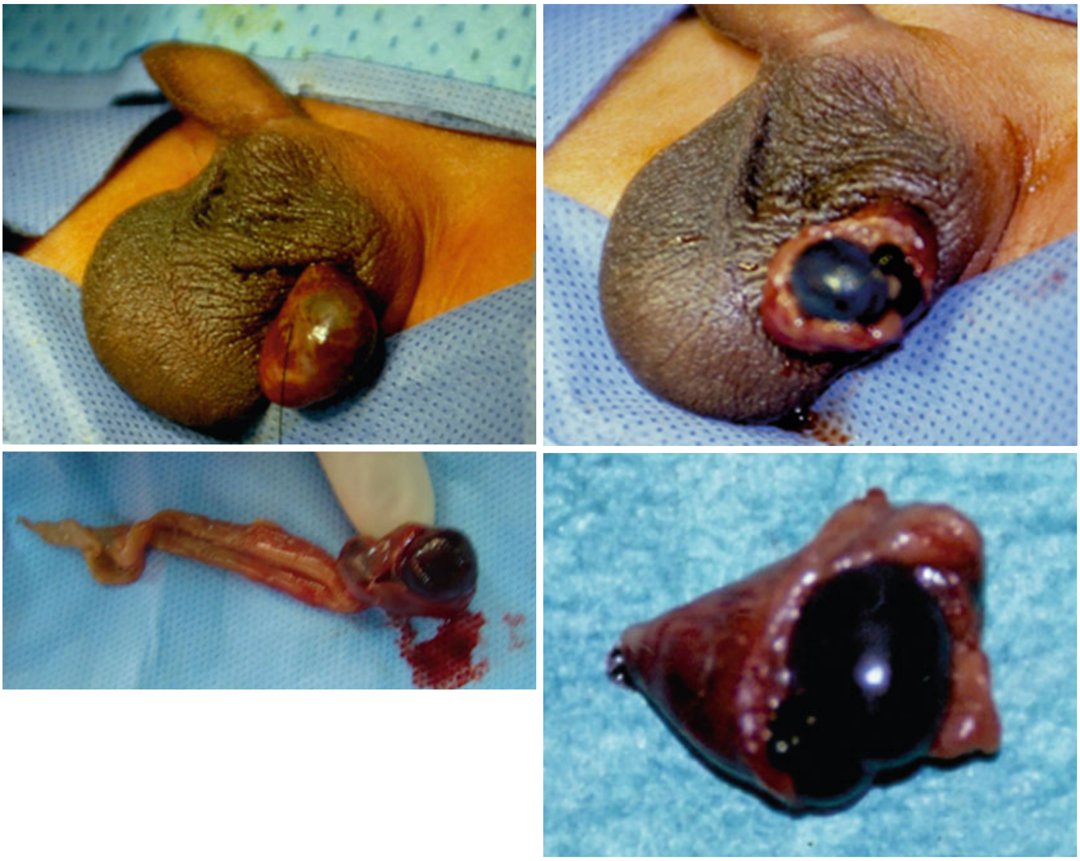
Figs. 26.12 and 26.13 Clinical intraoperative photographs showing intrauterine testicular torsion. Note the site of torsion which is extravaginal



Figs. 26.14 Clinical intraoperative photograph showing a completely gangrenous left testis following intrauterine torsion. The right testi was also necrotic (Bilateral torsion)

26.9.3 Clinical Features

- Commonly, these patients present immediately after birth.
- Prenatal, the usual presentation of extravaginal torsion is (Figs. 26.15, 26.16, 26.17, and 26.18):
  - A hard
  - Nontender testis

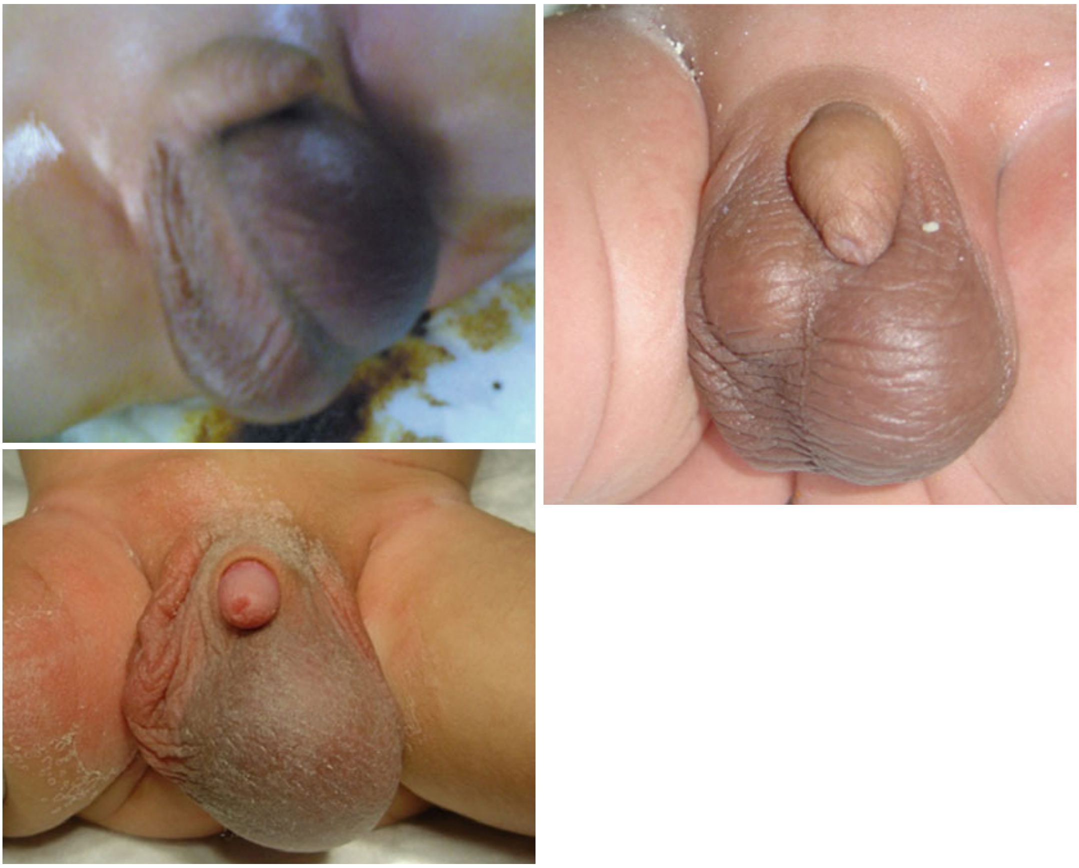


Figs. 26.15, 26.16, 26.17, and 26.18 Clinical intraoperative photographs showing intrauterine torsion of testes. Note the frankly necrotic testes

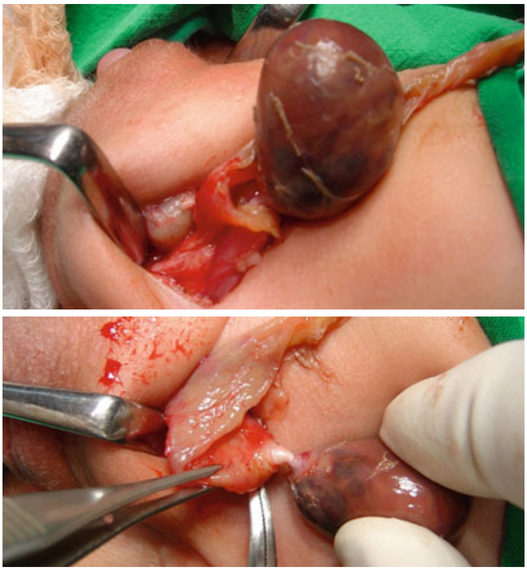
  - That is fixed to the overlying scrotal skin
  - Which is discolored
- It is thought that unilateral absence of the testis with blind-ending vessels is an indication of early in utero testicular torsion as hemosiderin is often found in the distal section of the spermatic cord.
- Acute scrotal swelling and tenderness without fixation to the scrotal wall, may represent a postnatal torsion with some hope of subsequent testicular salvage with surgical exploration.
- Prenatal testicular torsion manifests as (Figs. 26.19, 26.20, 26.21, 26.22, 26.23, 26.24, 26.25, and 26.26):
  - A firm, hard, scrotal mass
  - It does not trans illuminate
  - In an otherwise asymptomatic healthy newborn male
  - The scrotal skin characteristically fixes to the necrotic gonad
  - The scrotal skin is often discolored and the affected side often appear darker than the contralateral side

26.9.4 Treatment

- The treatment of neonatal torsion is still controversial (Figs. 26.27, 26.28, 26.29, and 26.30).
  - Some advocate elective exploration and contralateral orchidopexy because bilateral



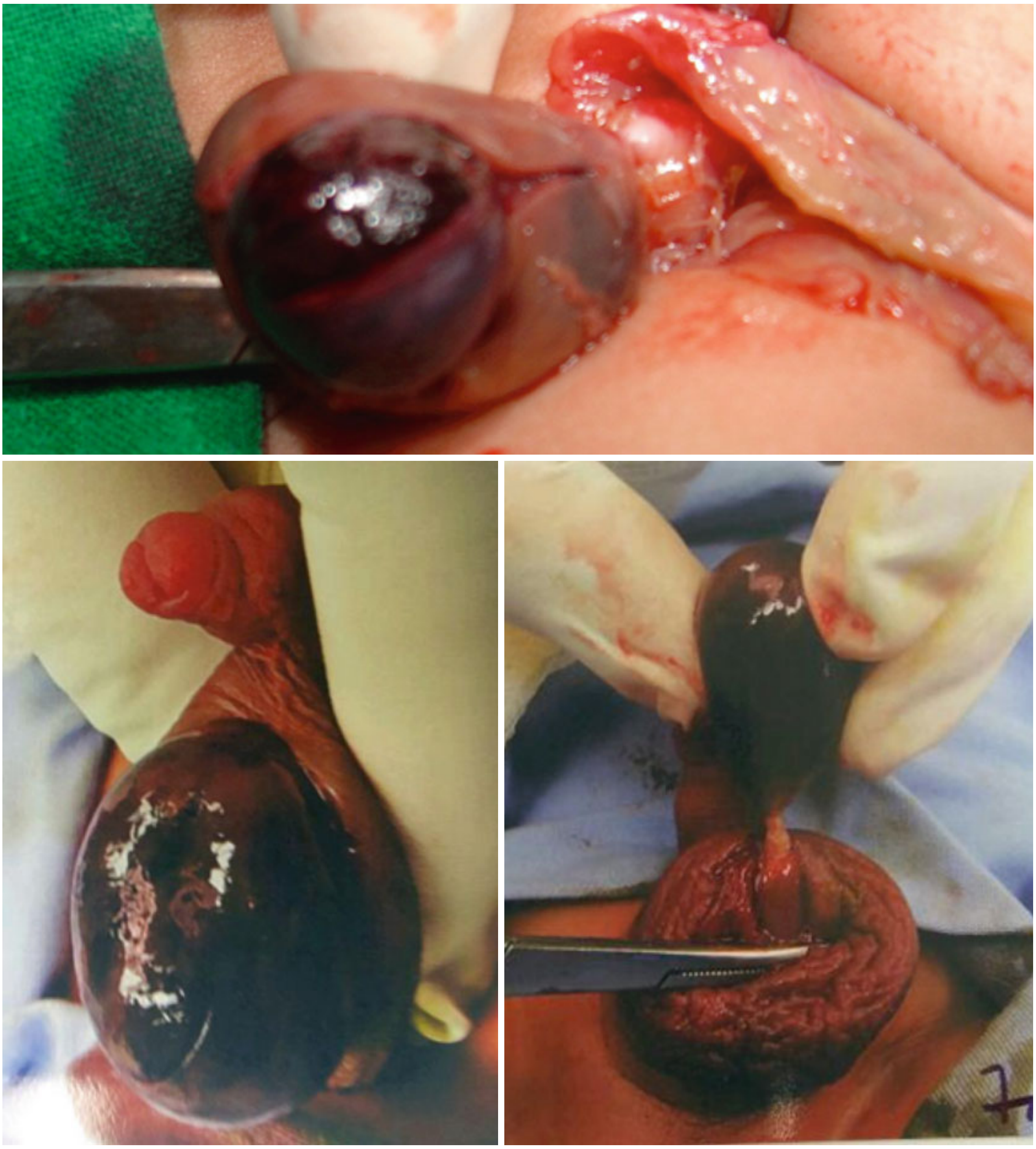
Figs. 26.19, 26.20, and 26.21 Clinical photographs of three newborns with testicular torsion. Note the discoloration of the scrotum. Note also the associated undescended right testis in the third patient



Figs. 26.22 and 26.23 Clinical intraoperative photographs showing intrauterine torsion of testis. Note the site of twist which is extravaginal

(synchronous or asynchronous) neonatal testicular torsion has been described.

- If the testis is necrotic, an orchiectomy and contralateral orchidopexy is performed.
- Retention of a necrotic testis may exacerbate the potential for subfertility, presumably because of development of an autoimmune phenomenon. This however is not fully supported.
- To prevent subsequent torsion on the other side contralateral orchiopexy is always performed.
- There are others who advocate emergency exploration.
  - The argument in favor of this is that the timing of testicular torsion is not exactly known and although the chance of saving the testis is small, this is worth doing.



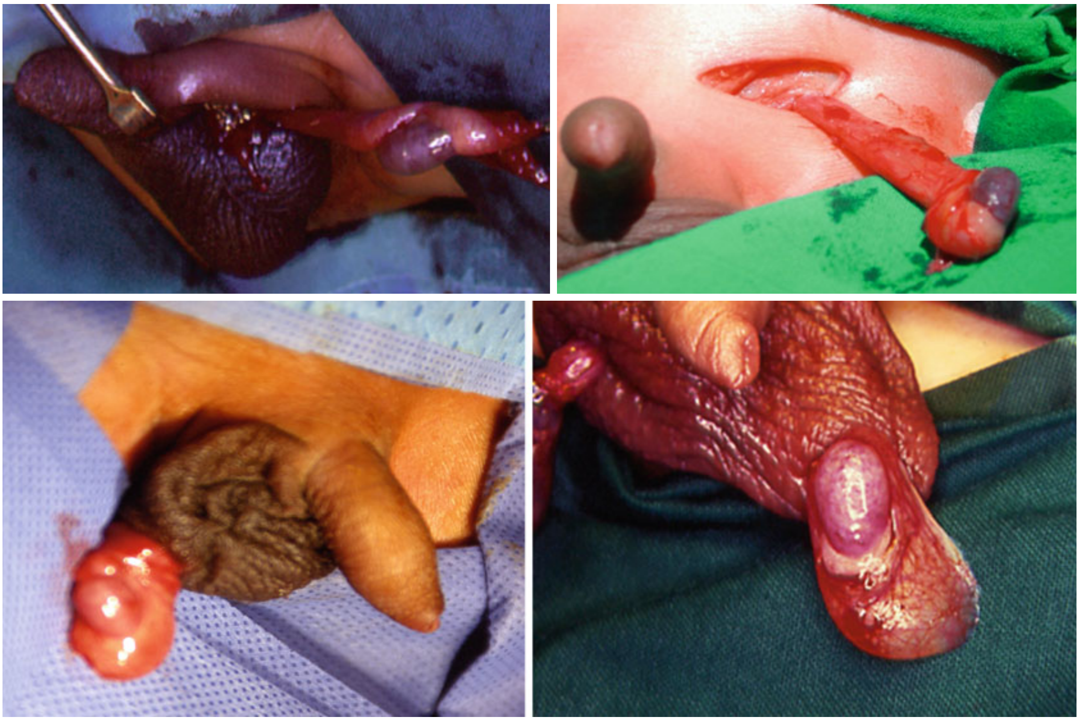
Figs. 26.24, 26.25, and 26.26 Clinical intraoperative photographs showing frankly necrotic testes following intrauterine torsion

- Add to this the fact that these patients are usually healthy of good size and currently the anesthesia is safe.
- Many authors feel that these patients should be managed with early exploration and if the testis is found necrotic, orchidectomy and contralateral orchidopexy is performed. If the testis is found viable, bilateral orchidopexy is performed.

26.10 Torsion of the Testicular or Epididymal Appendage

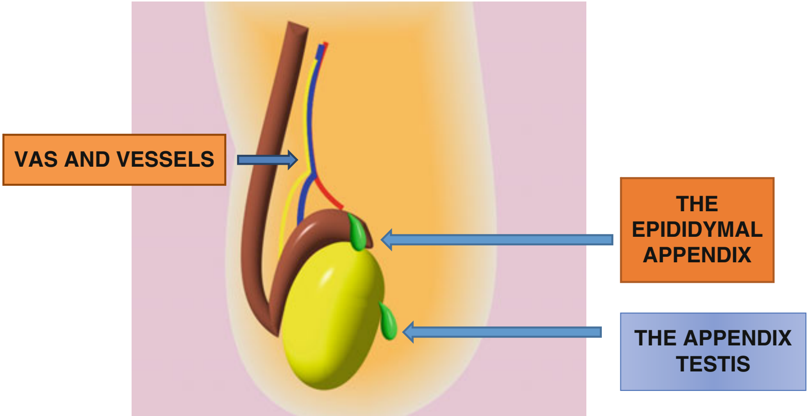
26.10.1 Introduction

- Torsion of testicular appendices is one of the most common causes of acute scrotum.
- It is considered the leading cause of acute scrotum in children.



Figs. 26.27, 26.28, 26.29, and 26.30 Clinical intraoperative photographs of four patients with intrauterine torsion. The testes were found congested and dusky but viable. All underwent bilateral orchidopexy. Early surgical exploration is important in these patients as the exact timing of torsion is not known and in some of these patients, torsion may occur at the time of delivery or shortly after

Fig. 26.31 Diagrammatic representation of the two common testicular appendages



- This is considered the most common cause of acute scrotal pain in boys aged 7–14 years.
- It can resemble testicular torsion but the onset of pain is more gradual.
- Systemic symptoms are rare.
- Localized tenderness occurs but only in the upper pole of the testis.
- In those with acute scrotal pain, the incidence of torsion of testicular appendage ranges from 46–71 %.
- Torsion of the testicular appendices is virtually a benign condition, but must be distinguished from testicular torsion (Fig. 26.31).

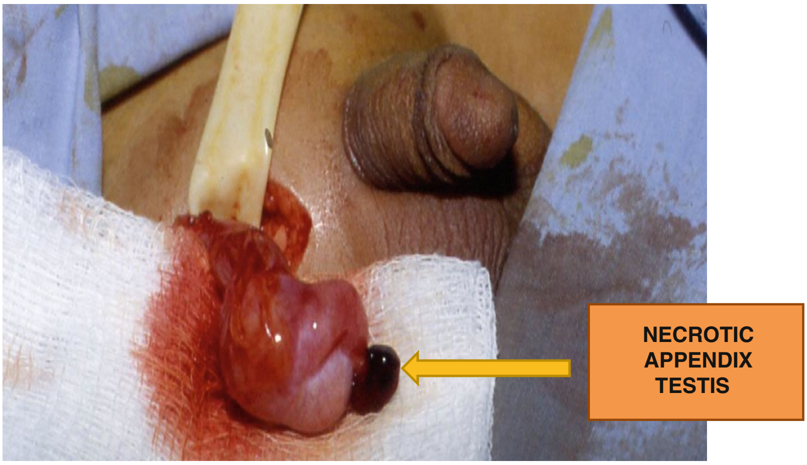


Fig. 26.32 An intraoperative photograph showing torsion of the appendix testis in a child

- The appendix testis and epididymal appendix are commonly pedunculated and because of this are predisposed to torsion.
- Torsion of either appendage (The appendix testis and Epididymal appendix) produces pain similar to that experienced with testicular torsion, but the onset is usually more gradual.

26.10.2 Embryology

- The appendix testis:
  - This is a Müllerian duct remnant.
  - It is present in 92 % of all testes.
  - It is located at the superior pole of the testis in the groove between the testis and epididymis.
  - It is the most common appendage to undergo torsion.
- The epididymal appendix:
  - This is a Wolffian duct remnant.
  - The appendix epididymis is present in 23 % of testes.
  - It is usually located on the head of the epididymis.
  - It is the second common appendage to undergo torsion.

26.10.3 Clinical Features

- The majority (80 %) of torsion of the testicular or epididymal appendage occurs in boys aged 7–14 years (Mean age 10.6 years).
- The usual presentation is acute scrotal pain but the onset is more gradual. This is important in distinguishing this from testicular torsion.
- The pain is more localized to the upper pole of the testis which is also tender.
- The pain is usually not associated with systemic symptoms, nausea, vomiting or urinary symptoms.
- Localized tenderness occurs but only in the upper pole of the testis.
- Usually, the scrotum appears normal but sometimes there is an associated erythema and edema.
- The cremasteric reflex is usually intact.
- Occasionally, a paratesticular nodule at the superior aspect of the testicle is present. This is called the blue-dot sign which is present in only 20 % of cases (Fig. 26.32).
- This is the appendix of the testis which has become discolored and is noticeably blue through the skin.

26.10.4 Investigations and Treatment

- Ultrasonography can be useful in distinguishing torsion of a testis and torsion of an appendix testis.
- Color Doppler ultrasonography is the imaging modality of choice for evaluation of the acute scrotum.

- This usually shows normal blood flow to the testis and sometimes an increase on the affected side due to inflammation.
- This is a self-limiting condition and most cases are treated conservatively.
- The treatment is conservative and the condition usually resolves within 2–3 days.
- Rarely surgery is indicated:
  - If it is difficult to differentiate from testicular torsion.
  - If the pain is severe and cannot be controlled by analgesics.
- The management includes:
  - Bed rest and scrotal elevation.
  - Nonsteroidal anti-inflammatory drugs and analgesics.
  - Torsion of a testicular appendage may be misdiagnosed as epididymitis but if the urinalysis is normal, no antibiotic therapy is required.
  - The inflammation usually resolves within a week.

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Testicular Tumors in Children

27

27.1 Introduction

- Testicular tumors are relatively rare in the pediatric age group.
- They account for only 1–2 % of all Pediatric Solid Tumors.
- Children represent only 2–5 % of all patients with testicular cancer.
- The exact incidence of testicular cancer is not known but it has been estimated at 5.5 cases per 100,000 men per year.
- Others reported an incidence of testicular cancer of 2.75–8 per 100,000 men per year.
- Testicular cancer rates are lowest in Asian and African populations, at less than 1 case per 100,000 men per year.
- Testicular cancer rates are highest in developed European countries at eight to nine cases per 100,000 men per year.
- Testicular tumors are more common in whites with a white-to-black incidence ratio of approximately 5:1.
- The highest rates of prevalence of testicular cancer is in Scandinavia, Germany, and New Zealand.
- Testicular cancers are considered the most common cancer in males aged 20–39 years.
- The median age for diagnosis of testicular cancer has been reported at 33 years.
- Testicular cancer is rarely seen before the age of 15 years.
- In the pediatric age group, the annual incidence of testicular cancer is approximately 1 in 100,000 male children per year.
- Others reported the incidence of testicular tumors in children to be only 1.6 per 1 million children-years.
- Testicular tumors are rare in children compared with testicular tumors occurring postpubertally or with other genitourinary tumors in childhood such as Wilms tumor (Figs. 27.1 and 27.2).
- The majority of testicular tumors occur in children <2 years of age.
- 75 % of testicular tumors occur before age 2.5 years.
- Benign Tumors Account for 38 % of all testicular tumors.
- However, there is actually a bimodal age distribution for testicular tumors with a large peak in young adults and a much smaller peak in the first 3 years of life.
- This bimodal age distribution reflects more fundamental differences between prepubertal and postpubertal testicular tumors.
- These differences include the typical tumor histology in each group, the malignant potential of tumors at different ages, and the molecular biological differences between prepubertal and postpubertal tumors.
- The most striking difference between prepubertal and postpubertal tumors is the incidence distribution of different tumor types.

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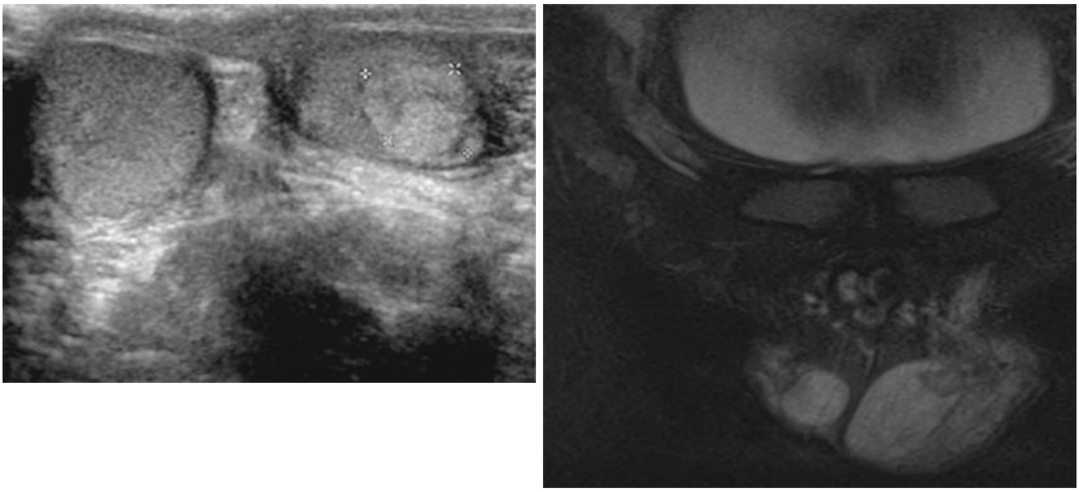
A.H. Al-Salem, *An Illustrated Guide to Pediatric Urology*, DOI 10.1007/978-3-319-44182-5_27



Figs. 27.1 and 27.2 Scrotal ultrasound and MRI showing left testicular tumor in a child. This proved to be a Leydig cell tumor

- Teratoma is considered the most common type in children.
- Undescended testes is a well-known risk of testicular cancer.
- Testicular cancer is two times to three times more common in boys undergoing prepubertal orchiopexy
- Postpubertal orchiopexy are two to six times more likely to develop testicular cancer than the general population.
- The relative risk of testicular cancer increases with age at orchiopexy.
- The relative risk of testicular cancer increases the higher the position of undescended testes.
- Others reported that 3.8 % of children with abdominal undescended testes, abnormal external genitalia, or abnormal karyotype develop testicular cancer.
- The relative risk of testicular cancer increases in those with bilateral cryptorchidism.
- 74 % of malignancies in persistent cryptorchid testes, are seminoma.
- 63 % of malignancies in post orchiopexy patients, are non-seminoma.
- There is no increased risk for tumors in the contralateral normally descended testis
- Other studies reported cancer in contralateral testis in 20 % of cases.
- Chromosomal Abnormalities (del(1p36)) are seen in 80 % of Yolk Sac Tumors
- Patients with Disorders of Sex Development (DSD) have increased incidence of testicular tumors.
- Hypovirilization and gonadal dysgenesis are at higher risk of developing testicular tumors.
- The presence of Y chromosome in gonadal dysgenesis increases the risk of testicular cancer to 10 % by age of 20.
- Intratubular germ cell neoplasia has been noted in 6 % of children with DSD.
- Germ cell testicular tumors are the most common solid tumors in men aged 15–35 years.

Testicular Cancer is Most Common Among Men Aged 15–40 Years, but it Has Three Peaks Depending on the Type

- Infants – 4 years of age: Teratomas and yolk sac tumors.
- 25–40 years of age: Seminomas and nonseminomas.
- 60 of age: Spermatocytic seminomas.

- The symptoms of testicular tumors may include one or more of the following:
  - Testicular swelling which may or may not be painful
  - Sharp or a dull aching pain in the lower abdomen or scrotum
  - Heaviness in the scrotum
  - Rarely, gynecomastia may develop from hormonal effects of β-hCG
  - Low back pain from tumor spread to the lymph nodes along the back
  - Shortness of breath and cough from metastatic spread to the lungs
- Pediatric prepubertal testicular tumors are dramatically different from adult neoplasms.
- Germ-cell tumors account for only 60–77 % of testicular tumors in children but account for 95 % of testicular tumors in adults.
- Adult germ-cell tumors with malignant potential, such as seminoma and embryonal carcinoma, are rarely seen in prepubertal patients.
- Testicular tumors are generally classified by the putative cell of origin.
- Testicular tumors are broadly classified into two main groups;
  - Germ-cell tumors
  - Stromal tumors
- In both children and adults, the vast majority of testicular tumors arise from germ cells.
- Seminoma, the most common germ cell tumor is considered a postpubertal tumor, although it has been reported in patients as young as 8 years.

Germ Cell Tumors Account for 95 % of Testicular Tumors in Adult but Only 60–77 % in Children and Include

- Seminomas
- Teratomas
- Embryonal carcinoma
- Choriocarcinomas
- Yolk sac tumors
- Mixed tumors.

- Seminomas comprise approximately 50 % of all germ cell tumors.
- Seminomas are generally believed to arise from the germinal epithelium of the seminiferous tubules because “seminoma cells” are morphologically similar to spermatogonia and also because seminomas are frequently found within the seminiferous tubules in early stages.
- Seminoma is confined to the testis in 85 % of patients at presentation.
- Unlike the nonseminomatous germ cell tumors, pure seminoma tends to remain localized or tends to involve only lymph nodes.
- It initially spreads to draining lymph nodes in the retroperitoneum and then spreads proximally to involve the lymphatics in the mediastinum and supraclavicular lymph nodes.
- Only rarely does pure seminoma spread hematogenously to involve lung parenchyma, bone, liver, or brain.
- Epidermoid cysts are generally considered a monodermal form of teratoma.
- Gonadoblastomas, which occur almost exclusively in the setting of disorders of sexual development, contain both germ cell and stromal elements.
- Mixed germ cell tumors which contain two or more histological types are particularly common in adolescents and adults whereas prepubertal germ cell tumors are virtually always of a single histological type.

Stromal Tumors

- Leydig cell tumor
- Sertoli cell tumor
- Juvenile granulosa cell tumor

- Testicular tumors may also be classified based on their clinical behavior as benign or malignant.
- Seminoma, embryonal carcinoma, choriocarcinoma and yolk sac tumors are malignant.

- Teratomas, which are uniformly benign in children, are often malignant in adults.
- Histologically, teratoma is often pure with diploid DNA content containing all three embryological germ layers (ectoderm, mesoderm, and endoderm).
- The most common germ-cell tumors are teratomas and yolk-sac tumors, which account for about 62 % and 26 % of testicular tumors, respectively.
- Some series report that teratomas, which most believe are vastly underreported because of their benign nature, may account for almost 50 % of prepubertal testicular tumors.
- However, in tumor registries, yolk-sac tumors are more common than teratomas, perhaps reflecting a reporting bias.
- Prepubertal teratomas account for less than 30 % of testicular germ-cell tumors in children and are uniformly benign.
- Most stromal tumors are benign, though occasionally malignant behavior is seen, particularly in older patients.
- The large majority of testicular tumors in adolescents and adults are malignant germ cell tumors – most commonly mixed germ cell tumors with pure seminomas occurring in older men.
- In contrast, the most common germ cell tumor in children is a benign teratoma.
- The most common malignant tumor in children is a yolk sac tumor, which is very rare in its pure form in post-pubertal patients.
- Overall, approximately 75 % of testis tumors in prepubertal patients are benign.
- Molecular biological and histological studies further support the distinct nature of prepubertal and postpubertal testis tumors.
- For example, chromosome 12 abnormalities are seen in nearly all adult malignant germ cell tumors, but are not seen in prepubertal yolk sac tumors which display abnormalities in other chromosomes.
- Intratubular germ cell neoplasia (ITGCN) which is frequently seen in the testicles of men with malignant germ cell tumors, does not occur in the setting of prepubertal yolk sac tumor.
- ITGCN is also generally absent in prepubertal testicles harboring a teratoma, while 88 % of testes removed for adult teratoma contain areas of ITGCN.
- These differences in histological distribution and clinical behavior have led to a divergence in the management strategies for prepubertal and postpubertal tumors.
- In children, a testis-sparing approach is becoming more common given the high incidence of benign tumors in this population.
- When a malignant tumor is identified, orchiectomy and observation with very selective use of chemotherapy has become the standard approach; retroperitoneal lymph node dissection (RPLND) and radiation therapy play a very limited role.
- Gonadal stromal tumors are significantly less common than germ-cell tumors (i.e. tumors of non–germ-cell origin) and primarily include juvenile granulosa-cell tumors, Leydig-cell tumors, and Sertoli-cell tumors.
- The vast majority (85 %) of yolk-sac tumors in children present as clinical stage I disease, compared with only 35 % in adults.
- An intratesticular lesion should be considered a malignancy unless proven otherwise.
- Scrotal sonography localizes the lesion and distinguishes a solid from a cystic mass.
- It can be extremely helpful in detecting small lesions within the testis, but its findings are not specific and by itself cannot exclude malignancy.
- A biopsy should not be performed, as it raises the risk of spreading cancer cells into the scrotum.
- Inguinal orchiectomy is the preferred method to treat testicular cancer.
- The lymphatic system of the scrotum is linked to the lower extremities, while the testicle lymphatics drain to the retroperitoneum.
- A transscrotal biopsy or orchiectomy will potentially lead to spread of cancer cells in the scrotum and subsequent spread to the inguinal nodes and further, while in an inguinal orchiectomy only the retroperitoneal route of spread exists.

- Alpha-fetoprotein (AFP) can be used as a reliable tumor marker because levels are increased in more than 90 % of yolk-sac tumors. Therefore, patients can be safely managed with observation after orchiectomy followed by chemotherapy for recurrent tumors.
- Retroperitoneal lymph node dissection is reserved for children with persistent retroperitoneal lymphadenopathy or increased serum tumor markers after orchiectomy and chemotherapy.
- Testis-sparing surgery with frozen section is a reasonable consideration for this and other benign prepubertal tumors. No follow-up is recommended for prepubertal teratomas, whereas postpubertal patients should be monitored into adulthood.
- Tumor excision without orchiectomy is particularly attractive in prepubertal patients because most tumors are benign in this population.
- An elevated AFP level in a child over 1 year of age virtually always reflects the presence of a yolk sac tumor and precludes a testis-sparing approach.
- For a testis-sparing approach, the testis is delivered into the inguinal incision (the cord having been occluded with a non-crushing clamp or vessel loop), the field is draped off with towels and the tunica vaginalis is opened. The tumor is excised or enucleated and sent for frozen section. If a benign histology is confirmed, then the testicular defect is closed with absorbable suture and the testis is returned to the scrotum. If a malignancy is detected, or the frozen section is nondiagnostic, then an orchiectomy is performed. Reports from small series suggest that this approach is safe and is effective in preserving testicular tissue.
- The lesions successfully treated with tumor enucleation (Testis-sparing surgery) included teratomas, epidermoid cysts, Sertoli cell tumors, and Leydig cell tumors.
- Adjuvant therapy:
  - Following excision of the primary tumor, universally benign tumors require no further evaluation or treatment.
  - Treatment options for potentially malignant tumors include surveillance, chemotherapy, retroperitoneal lymph node dissection (RPLND), and radiation therapy.
  - Virtually all germ cell tumors are sensitive to platinum-based multiagent chemotherapy which plays a major role in their management.
  - RPLND plays an important staging and therapeutic role for mixed germ cell tumors in adolescents, but is rarely employed in cases of prepubertal yolk sac tumor.
  - Radiation therapy is primarily used in treating seminoma – a very rare tumor in the pediatric population. The specific adjuvant therapy for a given patient is dependent on tumor histology and stage.
- Testicular cancer has one of the highest cure rates of all cancers:
  - If the cancer did not spread outside the testicle, the 5-year survival rate is 99 %.
  - If the cancer has grown into nearby structures or has spread to nearby lymph nodes, the 5-year survival rate is 96 %.
  - If the tumor has spread to organs or lymph nodes away from the tumor, the 5-year survival rate is around 74 %.

27.2 Classification of Testicular Tumors

- The most striking difference between prepubertal and postpubertal tumors is the incidence distribution of different tumor types.
- Testicular tumors are generally classified according to the cells of origin.
- Germ cell tumors include:
  - Seminoma
  - Embryonal carcinoma
  - Choriocarcinoma
  - Yolk sac tumor
  - Teratoma. Epidermoid cysts are generally considered a monodermal form of teratoma.
- Stromal tumors include:
  - Leydig cell tumor
  - Sertoli cell tumor
  - Juvenile granulosa cell tumor.

- Gonadoblastomas, which occur almost exclusively in those with disorders of sexual development, contain both germ cell and stromal elements.
- Mixed germ cell tumors which contain two or more histological types are particularly common in adolescents and adults whereas prepubertal germ cell tumors are virtually always of a single histological type.
- Testicular tumors may also be classified based on their clinical behavior as benign or malignant.
- Malignant testicular tumors include:
  - Seminoma
  - Embryonal carcinoma
  - Choriocarcinoma
  - Yolk sac tumors
  - Teratomas are universally benign in prepubertal patients, but may behave in a malignant fashion in adolescents and adults.
- Benign testicular tumors include:
  - Most stromal tumors are benign, though occasionally malignant behavior is seen, particularly in older patients.
  - The large majority of testicular tumors in adolescents and adults are malignant germ cell tumors – most commonly mixed germ cell tumors with pure seminomas occurring in older men.
  - In contrast, the most common germ cell tumor in children is a benign teratoma.
  - The most common malignant tumor in children is a yolk sac tumor, which is very rare in its pure form in post-pubertal patients.
  - Overall, approximately 75 % of testicular tumors in prepubertal patients are benign.
- Although testicular cancer can be derived from any cell type found in the testicles, more than 95 % of testicular cancers are germ cell tumors.
- Most of the remaining 5 % are sex cord-gonadal stromal tumors derived from Leydig cells or Sertoli cells.
- Correct diagnosis is necessary to ensure the most effective and appropriate treatment.

Classification of Testicular Tumors

- Testicular tumors are divided into two types:
  - Primary testicular tumors
  - Secondary testicular tumors
- Primary testicular tumors:
  - Germ cell tumors (95 %)
    - Seminomas (45 %)
    - Nonseminomas (50 %)
      - Mixed germ cell tumors (40 %)
      - Teratoma and teratocarcinomas (30 %)
      - Embryonal cell tumor (20 %)
      - Choriocarcinoma (1 %)
      - Yolk sac tumors (endodermal sinus tumors)
  - Non-germ cell tumors (5 %)
    - Stromal Leydig cell tumors
    - Sertoli cell tumors
- Gonadoblastoma
- Mixed Germ cell tumors
- Secondary testicular tumors:
  - Lymphoma, leukemia, and melanoma are the most common malignancies that metastasize to the testicle.

- Testicular tumors are also classified into:
  - Primary testicular tumors
  - Secondary or metastatic tumors
- The World Health Organization classification system for testicular tumors:
- Germ cell tumors
  - Precursor lesions
    - Intratubular germ cell neoplasia
      - Unclassified type (carcinoma in situ)
      - Specified types
  - Tumors of one histologic type (pure forms)
    - Seminoma
      - Variant – Seminoma with syncytiotrophoblastic cells
    - Spermatocytic seminoma
      - Variant – spermatocytic seminoma with sarcoma

    - Embryonal carcinoma
    - Yolk sac tumor
    - Trophoblastic tumors
      - Choriocarcinoma
        - Variant – monophasic choriocarcinoma
      - Placental site trophoblastic tumor
      - Cystic trophoblastic tumor
    - Teratoma
      - Variant – Dermoid cyst
      - Variant – Epidermoid cyst
      - Variant – Monodermal teratoma (Carcinoid, Primitive neuroectodermal tumor (PNET), Nephroblastoma-like tumor, others).
      - Variant – Teratomic with somatic-type malignancy
  - Tumors of more than one histologic type (mixed forms)
    - Embryonal carcinoma and teratoma
    - Teratoma and seminoma
    - Choriocarcinoma and teratoma and embryonal carcinoma
    - Others
- Sex cord/Gonadal stromal tumors
  - Leydig cell tumor
  - Sertoli cell tumor
    - Lipid rich variant
    - Scleriosing variant
    - Large cell calcifying variant
    - Intratubular sertoli cell neoplasia in Peutz-Jeghers syndrome
  - Granulosa cell tumour
    - Adult type
    - Juvenile type
  - Thecoma Fibroma Group
  - Sex cord/gonadal stromal tumor – incompletely differentiated
  - Sex cord/gonadal stromal tumour – mixed types
    - Thecoma
    - Fibroma
- Mixed Germ Cell and Sex Cord/Gonadal Stromal Tumors
  - Gonadoblastoma
  - Germ cell-sex cord/gonadal stromal tumour, unclassified
- Miscellaneous tumors of the testis
  - Carcinoid
  - Tumors of ovarian epithelial types
    - Serous tumour of borderline malignancy
    - Serous carcinoma
    - Well differentiated endometrioid tumour
    - Mucinous cystadenoma
    - Mucinous cystadenocarcinoma
    - Brenner tumour
  - Nephroblastoma
  - Paraganglioma
- Haematopoietic tumors
- Tumors of collecting ducts and rete
  - Adenoma
  - Carcinoma
- Tumors of the paratesticular structures
  - Adenomatoid tumour
  - Malignant and Benign Mesothelioma
  - Adenocarcinoma of the epididymis
  - Papillary cystadenoma of the epididymis
  - Melanotic neuroectodermal tumour
  - Desmoplastic small round cell tumour
- Mesenchymal tumors of the spermatic cord and testicular adnexae
  - Lipoma
  - Liposarcoma
  - Rhabdomyosarcoma
  - Aggressive angiomyxoma
  - Angiomyofibroblastoma-like tumour (see Myxoma)
  - Fibromatosis
  - Fibroma
  - Solitary fibrous tumour
  - Others
- Secondary tumors of the testis
- The most common type of testicular tumor in children is the germ cell tumors.
- Endodermal sinus tumor (yolk sac tumor) and teratomas are the most common germ cell tumors among all testis tumors in children.
- These tumors present with a malignant behavior sometimes. These tumors spread to the lung, retroperitoneal lymph nodes, bone, or the central nervous system.
- The most common malignant tumor is usually the endodermal sinus tumor in children.

- Teratomas are the most common benign tumors in children.
- Recent reports found that teratomas were more common than endodermal sinus tumors in children.
- The gonadal stromal tumors are usually benign, there has been the very rare case of malignant gonadal stromal tumor.
- Juvenile granulosa cell tumors are the most common tumors among neonatal tumors. These tumors are benign.

27.3 Histologic Classification of Seminomas

Classification of Testicular Tumors

- Germ Cell Tumors
  - Seminomas
  - Teratomas
  - Embryonal carcinoma
  - Choriocarcinomas
  - Yolk sac tumors (Endodermal sınus tumor)
  - Mixed germ cell tumors.
- Gonadal Stromal Tumors
  - Leyding cell
  - Sertoli cell
  - Juvenile granuloza gell
- Mixed form
- Gonadoblastoma
- Tumors of Supporting Tissues
  - Fibroma
  - Leimiyoma
  - Hemangioma
- Lymphomas and Leukemias
- Tumor like Lesions
- Epidermoid cysts
- Hyperplastic nodule secondary to congenital adrenal hyperplasia
- Secondary Tumors

- Grossly, seminomas are pale gray–to-yellow nodules that are uniform or slightly lobulated.
- Pure seminomas are subdivided into three subtypes based on histopathologic characteristics:

Histologic Classification of Seminomas

- Classic seminomas (85 %)
- Anaplastic seminoma (10 %)
- Spermatocytic seminoma (5 %)

- Classic seminomas (85 %):
  - They demonstrate a monotonous sheet of large cells with abundant cytoplasm and round hyperchromatic nuclei with prominent nucleoli.
  - A lymphocytic infiltrate or granulomatous reaction with giant cells or both is frequently present.
  - Trophoblastic giant cells capable of producing hCG are present in 15–20 % of tumors.
  - Mitoses are infrequent.
- Anaplastic seminoma (10 %):
  - This is an older term used to describe seminomas with three or more mitotic figures per high-power field.
  - This finding has no clinical or prognostic significance because the response of anaplastic seminomas to standard therapy is equivalent to that of classic seminomas.
- Spermatocytic seminoma (5 %):
  - This is a rare histologic variant that is not associated with carcinoma in situ.
  - These well-differentiated tumors usually contain cells resembling secondary spermatids or spermatocytes.
  - Spermatocytic seminomas rarely metastasize, and they occur almost exclusively in elderly men.
  - The only recommended treatment is orchiectomy.

27.4 Etiology of Testicular Tumors

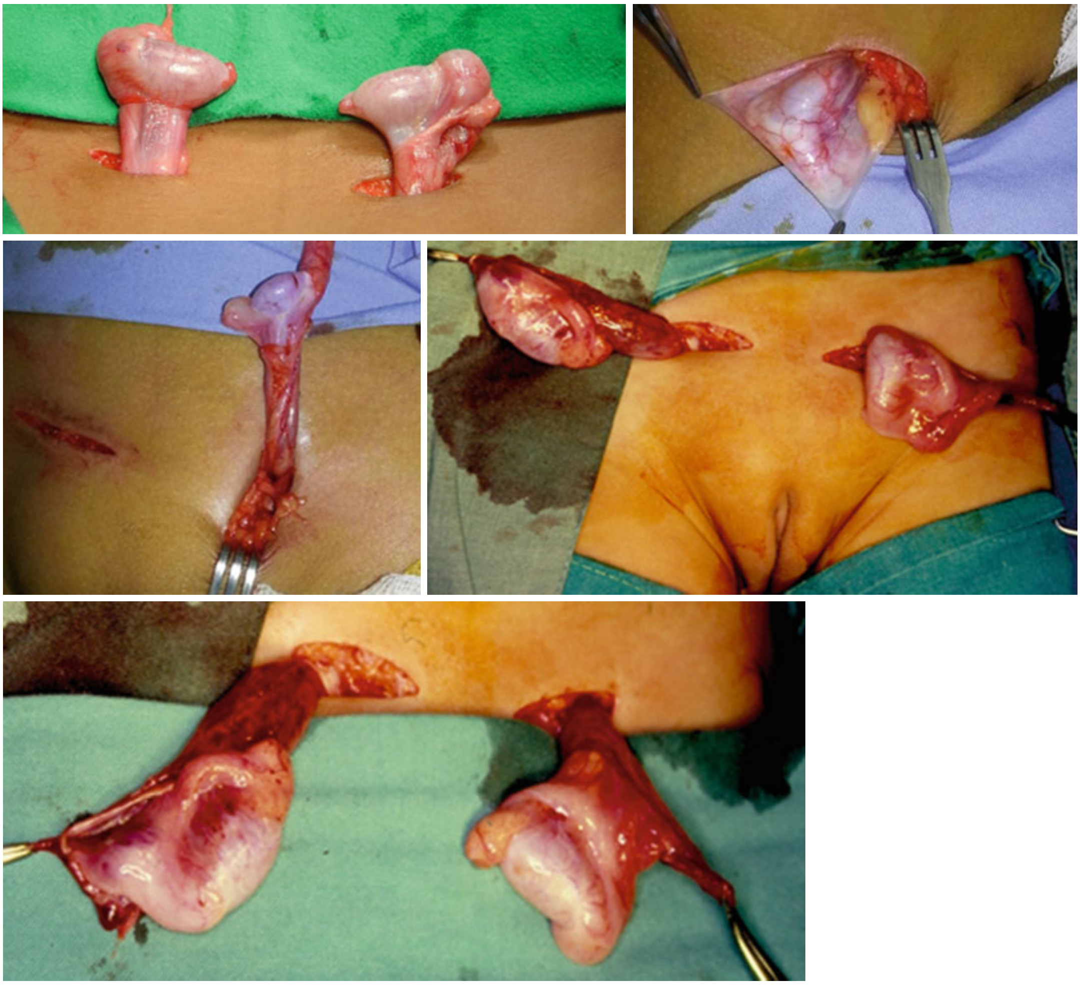
- The exact etiology of testicular cancer is not clearly known.
- There is a dramatic increase in the incidence rate of testicular cancer in developed countries and the reason for this is not known.

- Most testicular tumors occur sporadically, but familial cases have been observed and some cases occur because of a predisposing history.

Risk Factors for Testicular Cancer

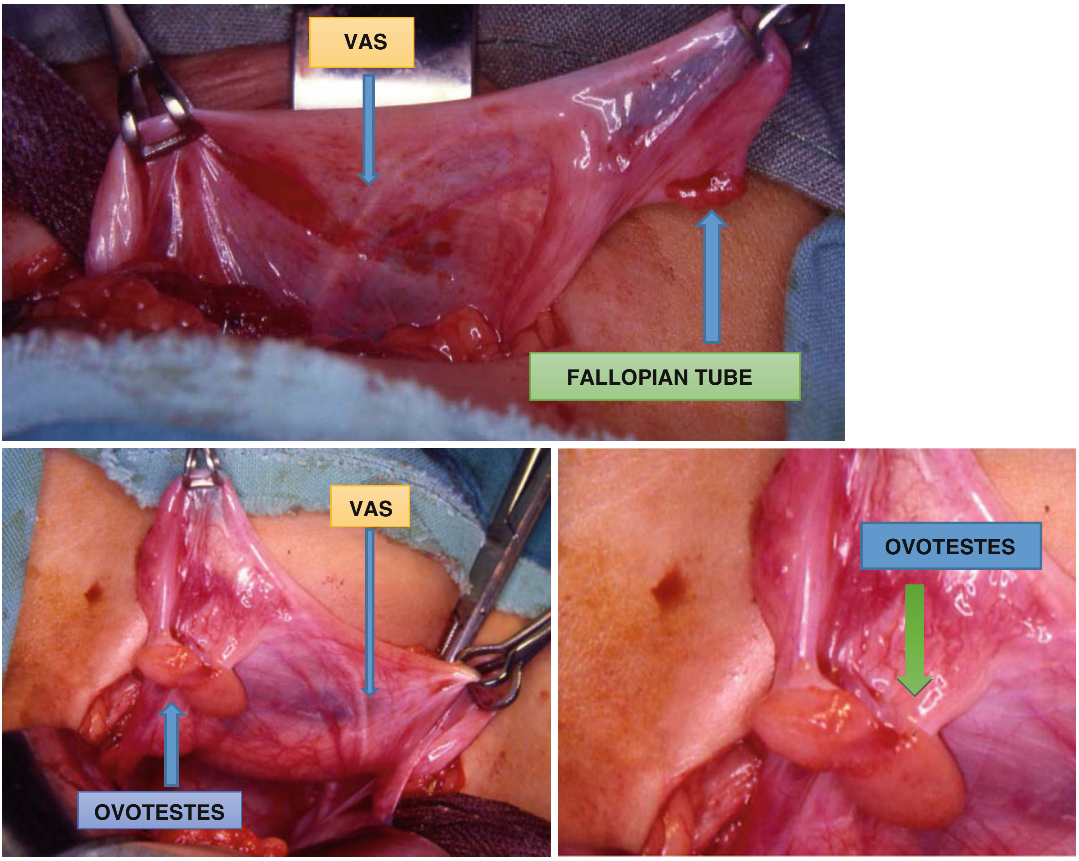
- Cryptoorchidism
- Testicular microlithiasis
- Disorders of sexual development
- Familial predisposition
- Other associations:
  - Iguinal hernias
  - Klinefelter syndrome
  - Mumps orchitis
  - Hypospadias and hydrocele
  - Chromosome 12 abnormalities
  - Prior testicular cancer increases the risk on the contralateral testis
  - Human immunodeficiency virus (HIV) infection
  - History of testicular trauma
  - Immunosuppression after organ transplant
  - Prior vasectomy
  - The use of cannabis and marijuana
  - An association with prenatal exposure to diethylstilbestrol (DES) has been postulated but not demonstrated

- A major risk factor for the development of testis cancer is cryptorchidism (undescended testicles).
  - The risk of testicular cancer in men with a history of undescended testis has been estimated at 10 to 40-fold greater than the general population.
  - More recent studies have found the risk to be fivefold greater than that of the general population.
  - The life-time risk for testicular cancer in those with undescended testis is 1–2 %.
  - 7–10 % of testis tumors occur in association with cryptorchidism.
  - 25 % of the cancers found in association with cryptorchidism occur in the contralateral, normally descended testis. This suggests that an inherent developmental defect is responsible for both the undescended testes and the tumor development.
  - It has been found that the risk of developing testicular cancer in patients with undescended testes is directly related to the degree of maldescent.
    - The risk is 1 in 20 if the testis is intra-abdominal.
    - The risk is 1 in 80 if it is within the inguinal canal.
  - Whether early orchidopexy can ameliorate that risk is unclear. Currently, it is believed that orchiopexy performed before puberty reduces the risk of germ cell tumors and improves the ability to observe the testis.
  - The increased risk of germ cell tumors is reflected in the finding of carcinoma in situ in 2–4 % of men with a history of cryptorchidism.
- Testicular microlithiasis:
  - Testicular microlithiasis refers to the presence of microcalcifications, usually diffuse, within the parenchyma of the testis on ultrasound.
  - Testicular microlithiasis is defined as ≥5 or more microcalcifications within a testicle.
  - Teticular microlithiasis is found incidentally in approximately 2 % of boys and men undergoing testicular ultrasound evaluation.
  - This has been identified as a possible risk factor for the development of testicular cancer but the reason for this association is not clear.
  - The association with testicular malignancies was suggested by the finding that approximately 25 % of adult testes harboring cancer are found to have testicular microlithiasis.
- Disorders of sexual development (Figs. 27.3, 27.4, 27.5, 27.6, 27.7, 27.8, 27.9, and 27.10):
  - Disorders of sexual development are a very significant risk for the development of gonadal tumors.
  - Some disorders, such as complete androgen insensitivity syndrome, have an increased risk of testicular cancer.



Figs. 27.3, 27.4, 27.5, 27.6, and 27.7 Clinical intraoperative photographs showing patients with testicular feminization syndrome. These are genotypically males with phenotypic female external genitalia. These patients usually have intraabdominal testes which are at increased risk of malignant transformation and must be removed

  - There is an increased risk in those with dysgenetic or streak gonads.
  - This risk seems to exist almost exclusively in patients with Y chromatin.
  - Patients with pure gonadal dysgenesis and Y chromatin as well as the “streak” gonad of patients with mixed gonadal dysgenesis are at a 15–30 % risk for tumor development.
  - The tumors arising in those with gonadal dysgenesis are usually gonadoblastomas.
  - While gonadoblastomas are benign, they are prone to the development of malignant degeneration and when malignancies occur, dysgerminoma is the most common histological type. .
  - While most cases of malignancy occur after puberty, there have been case reports in children as well.
  - Prophylactic removal of dysgenetic gonads should be undertaken early in life to avoid malignant transformation in these patients.
- Other risk factors include:
  - Inguinal hernias
  - Klinefelter syndrome
  - Mumps orchitis
  - Hypospadias and hydrocele



Figs. 27.8, 27.9, and 27.10 Clinical intraoperative photographs of a patient with ovotesticular DSD. Note the presence of an ovotestis on this side. The testis or testicular part of an ovotestis is likely to be dysgenetic with a risk of developing dysgerminomas, seminomas, gonadoblastomas, and yolk sac carcinomas

  - Chromosome 12 abnormalities are seen in nearly all adult malignant germ cell tumors, but are not seen in prepubertal yolk sac tumors.
  - Prior testicular cancer is a major risk factor for a contralateral malignancy. The cumulative risk 25 years after original diagnosis is 3.6 % for patients with seminoma.
  - Human immunodeficiency virus (HIV) infection
  - History of testicular trauma
  - Immunosuppression after organ transplant
  - Prior vasectomy
  - The higher rates of testicular cancer in western nations have been linked to use of cannabis. Long term use of cannabis and marijuana is linked to an increased risk for testicular cancer.

27.5 Clinical Features

- The incidence of pediatric testicular tumors peaks in children aged 2–4 years.
- Most yolk-sac tumors occur in children younger than 2 years.
- About 85 % of children with testicular tumors present with painless scrotal swelling.
- A few present with a hydrocele, scrotal pain, or a history of trauma, any of which probably alerts the child to the presence of a painless and enlarged testicle.
- 10 % may give a history of hernia or hydrocele
- 15–50 % have hydrocele on physical exam
- Rarely, they may present with acute abdominal pain

- The majority of testis tumors present as a palpable testicular mass.
- This can be detected by the patient, a parent, or by a physician on routine physical examination.
- Occasionally the patients present with a hydrocele.
- About 10–25 % of patients with a malignant tumors present with a hydrocele.
- Therefore, if a child presents with a hydrocele that clearly obscures physical examination of the testis, an ultrasound should be done to exclude an associated tumor.
- Rarely, patients may present with testicular pain.
- Signs related to metastatic disease are uncommon in children as the most common sites – the retroperitoneum and lungs – rarely result in physical findings.
- The most common presenting symptom in a patient with seminoma is a painless testicular mass. Other symptoms can include testicular pain (45 %) or heaviness.
- A history of previous testicular trauma is common. The trauma typically draws the patient's attention to the mass and not a cause.
- Seminoma that has spread to retroperitoneal lymph nodes can cause back pain or abdominal discomfort.
- Widely disseminated metastatic disease to lungs, liver, bone, or brain is rare but may produce systemic symptoms.
- A history of cryptorchidism or other genitourinary anomalies can be elicited in some patients.
- Once a testis tumor is suspected, a thorough physical examination is undertaken.
- Physical examination usually reveals a painless scrotal swelling with a hard mass or associated hydrocele.
- Some hormonally active tumors may appear in association with precocious puberty or gynecomastia.
- A hard mass may be palpable on physical examination. However, normal physical findings are not sufficient to exclude a tumor.
- In most cases the general examination will be normal.
- But occasionally signs of androgenization or other physical findings will be present suggesting a particular tumor type or advanced disease.

27.6 Staging

- In the Children's Oncology Group staging system:
- Stage I:
  - Patients with locally confined disease, negative radiographic studies, and the expected decline in tumor markers post-operatively.
- Stage II:
  - Patients with microscopically positive margins in the scrotum or spermatic cord and/or with persistently elevated tumor markers after orchiectomy. Patients who underwent transcrotal biopsy prior to orchiectomy at a separate setting are also considered stage 2.
- Stage III:
  - Patients with retroperitoneal lymphadenopathy.
- Stage IV:
  - Patients with distant metastases (most commonly in the lungs).
- Adolescents with germ cell tumors are generally staged as adults utilizing the TNM system of the American Joint Committee on Cancer and the International Union Against Cancer.

The Children's Oncology Group Staging System

- Stage I: Patients with locally confined disease, negative radiographic studies, and the expected decline in tumor markers post-operatively.
- Stage II:
  - Patients with microscopically positive margins in the scrotum or spermatic cord and/or with persistently elevated tumor markers after orchiectomy.
  - Patients who underwent transcrotal biopsy prior to orchiectomy at a separate setting.
- Stage III: Patients with retroperitoneal lymphadenopathy.
- Stage IV: Patients with distant metastases (most commonly in the lungs)

- Testicular seminoma is staged according to the American Joint Committee on Cancer (AJCC) 2010 staging guidelines.

- This is a TNM staging system comprising separate categorizations for the primary tumor, regional lymph nodes, distant metastases, and serum tumor markers.
- These four categories are used to determine the stage of the patient's disease.
- Modern treatment decisions are based, in part, on the subdivisions of this staging system.
- Primary tumor staging
  - Tis – Intratubular germ cell neoplasia (carcinoma in situ)
  - T1 – Tumor limited to testis/epididymis without vascular or lymphatic invasion; tumor may invade into the tunica albuginea but not the tunica vaginalis
  - T2 – Tumor limited to testis/epididymis with vascular or lymphatic invasion or tumor extending through tunica albuginea with involvement of the tunica vaginalis
  - T3 – Tumor invading spermatic cord with or without vascular/lymphatic invasion
  - T4 – Tumor invading scrotum with or without vascular/lymphatic invasion

The Intergroup Staging System for Testicular Germ Cell Tumors

- Stage I: Tumor limited to the testis and completely resected (85 % of children <4 years present with stage I disease, whereas only 35 % of adults with testicular tumors present with stage I)
- Stage II: Tumor removed by transscrotal orchiectomy, involvement of scrotum or spermatic cord, persistently elevated tumor markers.
- Stage III: Retroperitoneal lymph node involvement (≤2 cm, no visceral or extra-abdominal involvement)
- Stage IV: Distant metastases

27.6.1 Regional Lymph Node Staging

- N0 – No regional lymph node metastases
- N1 – Metastasis with lymph node(s) 2 cm or less in greatest dimension or multiple lymph nodes, none more than 2 cm in greatest dimension
- N2 – Metastasis with lymph node(s) larger than 2 cm but not larger than 5 cm in greatest dimension, or multiple lymph nodes, any one mass larger than 2 cm, but not more than 5 cm, in greatest dimension
- N3 – Metastasis with lymph node(s) larger than 5 cm in greatest dimension
- Distant metastatic staging
  - M0 – No distant metastases
  - M1a – Nonregional nodal or pulmonary metastasis
  - M1b – Distant metastases other than M1a
- Serum tumor marker staging
  - S0 – Marker studies within normal limits
  - S1 – LDH level less than 1.5 times the reference range, beta-hCG level less than 5000 mIU/mL, and AFP level less than 1000 ng/mL
  - S2 – LDH level 1.5–10 times the reference range, beta-hCG level 5000–50,000 mIU/mL, or AFP level 1000–10,000 ng/mL
  - S3 – LDH level more than ten times the reference range, beta-hCG level more than 50,000 mIU/mL, or AFP level more than 10,000 ng/mL

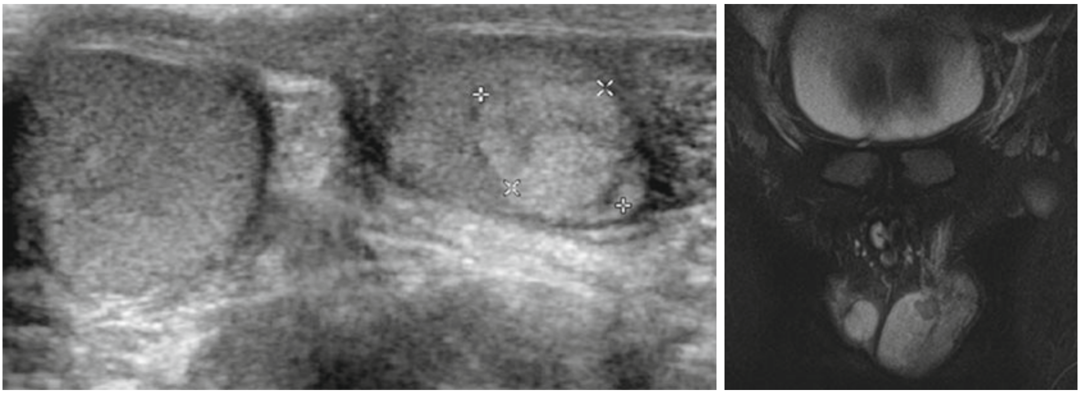
Children's Oncology Group Staging System for Yolk Sac Tumors

- Stage I:
  - Limited to testis
  - Completely resected by high inguinal orchiectomy
  - Tumor markers negative
  - Unknown tumor markers at diagnosis
  - Need negative ipsilateral retroperitoneal lymph node biopsy if >2 cm on CT
- Stage II:
  - Microscopic residual disease
  - Tumor markers remain elevated
  - Tumor rupture or scrotal biopsy prior to complete orchiectomy
- Stage III:
  - Retroperitoneal lymph node involve987`ment
  - (>4 cm on CT)
  - RPLN <4 cm, but >2 cm need biopsy
- Stage IV: Distant Metastasis

- Stage grouping:
  - Stage IA – T1 N0 M0 S0
  - Stage IB – T2, 3, 4 N0 M0 S0
  - Stage IS – Any T N0 M0 S1, 2, 3
  - Stage IIA – Any T N1 M0 S0, 1
  - Stage IIB – Any T N2 M0 S0, 1
  - Stage IIC – Any T N3 M0 S0, 1
  - Stage IIIA – Any T Any N M1a S0, 1
  - Stage IIIB – Any T Any N M0, 1a S2
  - Stage IIIC – Any T Any N M1a, 1b S3

27.7 Investigations

- CBC and differential.
- Liver function tests, electrolytes, BUN and creatinine.
- A chest x-ray or chest CT will identify pulmonary metastases.
- 20 % of yolk-sac tumors may present with metastases to the lung.
- Measurements of alpha-fetoprotein (AFP), human chorionic gonadotropin (beta-hCG), and lactate dehydrogenase (LDH) are important in the management of patients with testicular tumors such as seminomas.
- Tumor marker levels are used to assess response to treatment and to predict the likelihood of complete remission.
- Lactate dehydrogenase: The LDH level is an independent prognostic factor in patients with germ cell tumors (including seminoma). It is thought to reflect tumor burden.
- Tumor markers:
  - These are important in the evaluation of testis tumors in children and adolescents.
  - Both human chorionic gonadotropin (HCG) and alpha-fetoprotein (AFP) are important tumor markers.
  - Yolk sac tumors do not elaborate HCG, and AFP is the only important tumor marker in prepubertal patients.
  - AFP is a glycoprotein typically associated with the human fetus. AFP is found in nonseminomatous germ cell tumors, as well as in hepatocellular carcinomas, cirrhosis, hepatitis, and pregnancy.
  - The half-life of AFP is approximately 5 days.
  - Elevated AFP levels are rare in pure seminomas and indicate that nonseminomatous elements are also present (i.e., mixed tumor).
  - AFP is elaborated by 90 % of yolk sac tumors in children.
  - It is important to note that serum AFP levels can normally be as high as 50,000 ng/mL in the newborn dropping to approximately 300 ng/mL by 2 months of age. AFP levels do not achieve “normal” values until nearly 1 year of age.
  - Therefore, while an elevated AFP in a child over 1 year old with a testis tumor almost always reflects the presence of a yolk sac tumor, an “elevated” level in infants can occur in the setting of a benign tumor.
  - The post-operative value of tumor markers is also important.
  - Tumor marker serum levels should fall at a predictable rate based on the biological half-life of each marker (approximately 5 days for AFP and 48 h for HCG).
  - Failure of the markers to decline at the expected rate reflects the likely persistence of residual tumor.
  - Persistently elevated AFP levels after surgery suggest tumor metastases or recurrence.
  - Liver dysfunction can also cause false-positive elevations of AFP levels.
  - Beta-hCG is a glycoprotein typically produced by the placenta.
  - Elevations in beta-hCG levels are found in the serum of approximately 15 % of patients with seminoma.
  - The half-life of beta-hCG is approximately 22 h.
  - Serum testosterone levels may be elevated in Leydig-cell tumors.
  - Gonadoblastoma may elevate levels of beta-HCG.
- Scrotal, abdominal and pelvic ultrasound (Figs. 27.11 and 27.12):
- Imaging of the primary tumor almost always begins with ultrasonography.
- Ultrasound distinguishes testicular from extratesticular masses and the ultrasono-



Figs. 27.11 and 27.12 Scrotal ultrasound and MRI showing left testicular tumor. Histological evaluation showed this to be Leydig cell tumor

graphic appearance of specific testis tumors has been described.

  - The ultrasonographic features, while suggestive, are not diagnostic.
  - When the clinical findings and ultrasound are suggestive of malignancy, a computerized tomography (CT) scan of the abdomen and pelvis is obtained to identify retroperitoneal involvement.
  - Benign tumors tend to be well-circumscribed with sharp borders and decreased blood flow on Doppler studies.
  - Epidermoid cysts usually demonstrate echogenic debris within the well-defined cyst.
  - Yolk sac tumors tend to be more solid in appearance.
  - The typical testicular tumor is intratesticular and may produce one or more discrete hypoechoic masses or diffuse abnormalities with microcalcifications that can be detected.
  - Calcifications are more frequent in seminoma than in nonseminomatous tumors.
  - When the clinical findings and ultrasound are suggestive of a benign tumor, no further evaluation is undertaken.
- CT scan and MRI of the abdomen and pelvis (Figs. 27.11 and 27.12):
  - This is important in determining the extent of the tumor.
  - It is also valuable in identifying the presence and extent of retroperitoneal lymphadenopathy.
  - Retroperitoneal lymph nodes measuring 1–2 cm are confirmed to be pathologically involved with metastatic tumor in approximately 70 % of cases.
- Patients with rhabdomyosarcomas require chest radiography, abdominal-pelvic CT scanning, bone scanning, and bone-marrow aspiration.

27.8 Treatment

- A solid scrotal mass should be considered malignant until proved otherwise.
- Any suspicion of the testicular tumor warrants an inguinal approach to prevent scrotal violation by the tumor.
- High inguinal orchiectomy has been a standard surgical treatment.
- Current trends emphasize that testis-sparing surgery should be performed for benign lesions such as teratoma, leydig cell tumor, and epidermoid cyst based on frozen biopsy findings.
- The three basic types of treatment are surgery, radiation therapy, and chemotherapy.
- In most patients with testicular cancer, the disease is cured readily with minimal long-term morbidity.
- Stage 1 tumors: Orchiectomy followed by surveillance.
- Surveillance includes:
  - Frequent physical examinations.
  - Radiographic evaluation of the chest and retroperitoneum.

  - Serum tumor marker measurement.
  - Patients who developed metastatic disease are treated with two to four courses of multiagent platinum-based chemotherapy.
  - Patients who present with locally advanced disease, metastases, or persistently elevated serum tumor markers are similarly treated with multiagent platinum-based chemotherapy.
- An elevated AFP level in a child over 1 year of age virtually always reflects the presence of a yolk sac tumor and precludes a testis-sparing approach.
- However, in all infants, and in older children with a normal AFP, the likelihood of a benign tumor is considerable.
- This is also true in boys presenting with androgenization.
- However, in adolescents with normal tumor markers and an ultrasound appearance highly suggestive of a benign lesion, such as an epidermoid cyst, testis-sparing may be considered.
- A testis-sparing approach:
  - Through an inguinal approach.
  - The testis is delivered into the inguinal incision.
  - The cord is occluded with a non-crushing clamp or vessel loop.
  - The tunica vaginalis is opened.
  - The tumor is excised or enucleated and sent for frozen section.
  - If a benign histology is confirmed, then the testicular defect is closed with absorbable suture and the testis is returned to the scrotum.
  - If a malignancy is detected, or the frozen section is nondiagnostic, then an orchiectomy is performed.
  - Reports from small series suggest that this approach is safe and is effective in preserving testicular tissue.
  - The lesions successfully treated with tumor enucleation included:
    - Teratomas
    - Epidermoid cysts
    - Sertoli cell tumors
    - Leydig cell tumors
- While treatment success depends on the stage, the average survival rate after 5 years is around 95 %, and stage 1 cancers cases if monitored properly have essentially a 100 % survival rate.
- Inguinal orchiectomy:
  - The initial treatment for testicular cancer is surgery to remove the affected testicle.
  - This is to be done through an inguinal approach and never through the scrotum.
  - The lymphatic drainage of the scrotum is into the lower legs, while the lymphatic drainage of the testicles is into the abdomen and retroperitoneal lymph nodes.
  - For this reason, transscrotal testicular biopsy is not recommended.
- Retroperitoneal Lymph Node Dissection:
  - In the case of nonseminomas that appear to be stage I, retroperitonea lymph node dissection may be done to accurately determine whether the cancer is in stage I or stage II and to reduce the risk of metastasis to the retroperitonal lymph nodes.
  - This approach, while standard in many places, it is not the standard approach due to costs and the high level of expertise required to perform successful surgery.
- Adjuvant treatment:
  - Perhaps the greatest advance in the management of testicular cancer was the introduction of platinum-based chemotherapy.
  - Survival for both prepubertal and adult tumors has increased dramatically since its introduction.
  - Indeed, multiagent chemotherapy has become the standard therapy for virtually all metastatic prepubertal testicular malignancies.
  - Following excision of the primary tumor, universally benign tumors require no further evaluation or treatment.
  - Treatment options for potentially malignant tumors include surveillance, chemotherapy, retroperitoneal lymph node dissection, and radiation therapy.
  - Since testicular cancers can spread, patients are usually offered adjuvant treatment in the form of chemotherapy or radiotherapy.

  - The type of adjuvant therapy depends largely on the histology of the tumor and the stage of the tumor at the time of surgery.
  - If the cancer is not advanced, patients may be offered careful surveillance by periodic CT scans and blood tests, in place of adjuvant treatment.
  - For many patients with stage I cancer, adjuvant therapy following surgery may not be appropriate and patients will undergo surveillance instead.
  - This approach ensures that chemotherapy and or radiotherapy is only given to the patients that need it
  - Virtually all germ cell tumors are sensitive to platinum-based multiagent chemotherapy which plays a major role in their management.
  - Retroperitoneal lymph node dissection plays an important staging and therapeutic role for mixed germ cell tumors in adolescents, but is rarely employed in cases of prepubertal yolk sac tumor.
  - Radiation therapy is primarily used in treating seminoma – a very rare tumor in the pediatric population.
  - The specific adjuvant therapy for a given patient is dependent on tumor histology and stage.
  - The appropriate surgical treatment for any patient with suspected testicular tumor is radical inguinal orchiectomy with high ligation of the spermatic cord.
  - Transscrotal biopsy or transscrotal orchiectomy is inappropriate and should be avoided.
  - Adjuvant moderate-dose pelvic and/or paraaortic radiotherapy remains the standard treatment for patients with early-stage seminoma (stage I, IIA, or IIB) after orchiectomy.
  - Patients who are found to have more advanced disease (stage IIC, III, IV) have a high risk of systemic relapse if treated with surgery and radiation alone, and the standard treatment for these patients is combination chemotherapy.
- Radiation therapy:
  - Radiation may be used to treat stage 2 seminoma cancers, or as adjuvant therapy in the case of stage 1 seminomas, to minimize the likelihood of tumor spread.
  - Radiation therapy is ineffective and is not used to treat nonseminoma tumors.
- Chemotherapy:
  - Non-seminoma:
    - Chemotherapy is the standard treatment for non-seminoma when the cancer has spread to other parts of the body (that is, stage 2B or 3).
    - The standard chemotherapy protocol is three, or sometimes four, cycles of Bleomycin-Etoposide-Cisplatin.
    - An alternative, equally effective treatment involves the use of four cycles of Etoposide-Cisplatin.
    - Retroperitoneal lymph node dissection may also be performed after chemotherapy to remove masses left behind (stage 2B or more advanced), particularly in the cases of large nonseminomas.
  - Seminoma:
    - As an adjuvant treatment, the use of chemotherapy as an alternative to radiation therapy in the treatment of seminoma is increasing.
    - Radiation therapy appears to have more significant long-term side effects.
    - Two doses, or occasionally a single dose of carboplatin, typically delivered 3 weeks apart, is proving to be a successful adjuvant treatment.
    - Seminomas can recur decades after the primary tumor is removed. This calls for a close and long-term follow-up.

27.9 Yolk Sac Tumor

- Pure yolk sac tumors occur almost exclusively in infants and very young children.
- Histologic evaluation of the yolk-sac tumor demonstrates eosinophilic periodic acid-Schiff (PAS)–positive inclusions in the

cytoplasm of clear cells that consist of AFP and Schiller-Duval bodies.
- Nearly all are managed with surveillance or platinum-based chemotherapy.
- Current chemotherapeutic regimens for yolk-sac tumors are platinum-based protocols. Common agents include etoposide, bleomycin, and cisplatin.
- Follow-up should include monthly tests of serum AFP levels, chest radiography every 2 months for 2 years, and CT scanning or MRI of the retroperitoneum every 3 months for the first year and then biannually.
- Because spread to the retroperitoneal lymph nodes is uncommon, routine prophylactic dissection of the nodes is not performed.
- Chemotherapy is administered in patients with radiographic evidence of metastatic disease or persistently elevated serum AFP levels. The use of combination chemotherapy with cisplatin, etoposide, and bleomycin has been an effective treatment for metastatic disease, with a survival rate approaching 90 %.
- More than 99 % of all patients with yolk-sac tumors are expected to survive.
- Retroperitoneal lymph node dissection, which plays a central role in the staging and therapy of adults with mixed germ cell tumors, is rarely employed in children.
- This is in part because prepubertal patients are less likely than adults to have metastases limited to the retroperitoneum.
- Furthermore 80 % of prepubertal patients have clinical stage 1 disease and fewer than 20 % will recur with no therapy beyond orchiectomy.
- Finally, the morbidity of retroperitoneal lymph node dissection is likely to be greater in children than in adolescents and adult.
- In children, retroperitoneal surgery is reserved for biopsy of radiographically equivocal nodes or for resection of a persistent retroperitoneal mass following chemotherapy.
- The specific management for patients with yolk sac tumor has been defined by several multicenter clinical trials.
- Stage 1 tumors are managed with orchiectomy followed by surveillance. Surveillance includes frequent physical examinations, radiographic evaluation of the chest and retroperitoneum, and serum tumor marker measurement.
- Patients who developed metastatic disease are treated with two to four courses of multiagent platinum-based chemotherapy.
- Patients who present with locally advanced disease, metastases, or persistently elevated serum tumor markers are similarly treated with multiagent platinum-based chemotherapy.
- The survival for all patients with this approach was nearly 100 %.

27.10 Teratoma

- While metastatic disease occurs in up to 60 % of adults with teratoma, these tumors are universally benign in pre-pubertal patients.
- Adolescents with teratoma should undergo orchiectomy and a metastatic evaluation followed by surveillance for stage 1 disease.
- Because of its benign nature, prepubertal teratoma can be managed with testis-sparing surgery.
- Teratomas and teratocarcinomas contain elements derived from more than one of the three germ tissues: endoderm, mesoderm, and ectoderm. These tumors are often cystic, and tissues such as skin, hair, bone, and even teeth may be present. Although they contain areas of poorly differentiated cells with a malignant appearance, teratomas are consistently benign in children younger than 2 years.
- The vast majority of prepubertal teratomas are “mature” teratomas, and for these tumors, no further treatment or follow-up is necessary.
- Immature teratomas are characterized by the presence of embryonal or incompletely differentiated tissue components, most commonly primitive neuroectodermal structures.
- There is some uncertainty regarding the behavior of immature teratomas.
- Pediatric immature teratomas (regardless of site) generally behave in a benign fashion if completely resected.
- Somatic malignancies may also arise in immature teratomas leading to metastatic spread. This is exceedingly rare in children.

- Furthermore, if foci of yolk sac tumor are found in an immature teratoma, then it should be treated as a yolk sac tumor.
- While immature teratomas of the testis can be managed with complete tumor resection alone, these patients should be followed-up.
- Epidermoid cysts are composed entirely of keratin-producing squamous epithelium and are universally benign in children and adults.
- They can be treated by tumor enucleation with no chemotherapy or follow-up.

27.11 Mixed Germ Cell Tumor

- Mixed germ cell tumors are rare in prepubertal patients, but account for a significant proportion of testis tumors in adolescents.
- These tumors are managed as adults with observation, retroperitoneal lymph node dissection and/or chemotherapy depending on the specific histology and stage of the disease.
- Patients with stage 1 mixed germ cell tumors may be managed with surveillance.
- The recurrence rate on surveillance is 25–30 %.
- Recurrence may be prevented with a modified nerve-sparing retroperitoneal lymph node dissection or two cycles of platinum-based chemotherapy, but this “over-treats” the 70–75 % of patients who do not have occult metastatic disease.
- On the other hand, when recurrence occurs on surveillance, more intense therapy is required.
- Patients with low risk disease are usually followed with frequent chest x-rays, tumor marker measurements and abdominal CT scans.
- Nearly all recurrences occur within 2 years of orchiectomy and are treated with chemotherapy.
- Patients at higher risk for recurrence generally undergo a modified nerve-sparing retroperitoneal lymph node dissection:
  - Those with vascular invasion
  - Largely embryonal cell histology
  - Those who are poorly compliant with therapy
- If microscopically positive nodes are found at the time of retroperitoneal lymph node dissection, these patients are treated with a course of chemotherapy.
- Patients with radiographic evidence of metastatic disease at presentation or persistently elevated tumor markers following orchiectomy are treated with three to four cycles of chemotherapy.
- The relapse rate following primary chemotherapy for metastatic disease is approximately 15 %, though it may be as high as 30 % for poor-risk patients.
- Retroperitoneal lymph node dissection may be considered for patients with very limited retroperitoneal lymph node disease at presentation and normalization of tumor markers after orchiectomy.
- Some patients with mixed germ cell tumors treated with chemotherapy for metastatic disease will have a residual retroperitoneal mass following therapy.
- If tumor markers have normalized, these residual masses should generally be resected.
  - 40–50 % of residual masses will contain only necrotic tissue and fibrosis.
  - 10–20 % will have persistent malignancy.
  - 40–45 % will contain mature teratoma.

27.12 Stromal Tumors

- Stromal tumors of the testis are rare in children and adolescents.
- Leydig cell tumors and juvenile granulosa cell tumors are universally benign in children.
- Leydig cell tumors:
  - These are the second most common gonadal stromal tumors in children and are also benign.
  - Leydig cell tumors usually present between 5 and 10 years of age with precocious puberty.
  - The synthesis of testosterone may produce precocious puberty, gynecomastia, and elevated levels of 17-ketosteroids.
  - Leydig-cell tumors must be differentiated from hyperplastic nodules that develop in

  boys with poorly controlled congenital adrenal hyperplasia (CAH).
  - They may be treated with orchiectomy or tumor enucleation.
  - Contralateral tumors may also occur, though they are rare in children.
- Adrenal rests:
  - Adrenal rests along the spermatic cord and in the testicular hilum may hypertrophy in patients with precocious puberty due to congenital adrenal hyperplasia mimicking a Leydig cell tumor.
  - In patients with congenital adrenal hyperplasia the nodules are often multifocal and bilateral.
  - The diagnosis of congenital adrenal hyperplasia can generally be made by demonstrating an elevated serum 17-hydroxyprogesterone level.
  - The nodules will usually resolve or significantly reduce in size with steroid replacement therapy for congenital adrenal hyperplasia. If this occurs, the patient may be followed with serial examinations.
  - Large nodules that fail to regress may be safely enucleated.
- Juvenile granulosa tumors:
  - These account for approximately 3 % of all neonatal testicular tumors and commonly appear as cystic, painless testicular masses.
  - Juvenile granulosa cell tumors occur almost exclusively in the first year of life, most commonly in the first 6 months.
  - Chromosomal mosaicism, structural abnormalities of the Y chromosome, and ambiguous genitalia are common in boys with juvenile granulosa cell tumor.
  - These tumors are hormonally inactive and benign.
  - Although these children should undergo a chromosomal analysis, the tumor itself may be treated by orchiectomy or tumor enucleation with no metastatic evaluation or adjuvant therapy.
- Sertoli cell tumors:
  - These are the most common gonadal stromal tumors in prepubertal children.
  - These tumors tend to appear as painless masses in boys younger than 6 months and produce no endocrinologic effects; however, 14 % of patients present with gynecomastia.
  - Approximately 10 % of adult Sertoli cell tumors are malignant, malignancy however is very rare in children.
  - All reported cases of Sertoli cell tumors in children under 5 years of age are benign but there have been a few cases of malignant Sertoli cell tumors in older children.
  - Therefore, children younger than 5 years are adequately treated with orchiectomy and do not require metastatic evaluation.
  - Older children should undergo chest radiography and abdominal CT scanning to rule out metastases.
  - Tumor excision is usually adequate treatment for infants, but a metastatic evaluation should be considered such as:
    - Large tumor size
    - Areas of necrosis
    - Vascular invasion
    - Cellular atypia
    - Increased mitotic activity.
  - Older children with Sertoli cell tumors should undergo a full metastatic evaluation.
  - Metastases are treated with a combination of radiotherapy, chemotherapy, and retroperitoneal lymph node dissection.
  - Large-cell calcifying Sertoli cell tumors:
    - These are clinically and histologically distinct tumors which occur predominantly in children and adolescents.
    - These tumors are composed of large cells with abundant cytoplasm and varying degrees of calcification.
    - Approximately one third of patients have an associated genetic syndrome and/or endocrine abnormality, the most common being Peutz-Jeghers syndrome and Carney's syndrome.
    - Peutz-Jeghers syndrome is an autosomal dominant disorder consisting of mucocutaneous pigmentation and hamartomatous intestinal polyposis.
    - Features of Carney syndrome include myxomas of the skin, soft tissue, and heart; myxoid lesions of the breast; lentigines of the face and lips; cutaneous

    blue nevi; Cushing syndrome; pituitary adenoma; and schwannoma.
    - Patients and first-degree relatives of patients with large-cell calcifying Sertoli cell tumor should be screened for these potentially serious syndromes.
    - Whereas these tumors are occasionally malignant in adults, they have been universally benign in patients under 25 years of age.
    - Orchiectomy is sufficient treatment in children, but approximately one fourth of patients will have bilateral and/or multifocal disease.
    - A testis-sparing approach has been described for this rare tumor.
- A mixed or poorly differentiated stromal tumor:
  - Rarely a prepubertal patient may have a mixed or poorly differentiated stromal tumor.
  - Most of these tumors are benign.
  - Malignancy should be considered in those with:
    - A large number of mitotic figures
    - A tumor that is poorly differentiated
    - Local invasion.
  - Orchiectomy is the treatment of choice.
  - Retroperitoneal lymph node dissection and adjuvant therapy are indicated in those with metastatic disease.
  - These patients should be followed-up closely for the development of metastatic disease.

27.13 Simple Testicular Cyst

- Simple testicular cysts may be observed but if large in size, they should be excised.
- Cystic dysplasia of the rete testis is a benign tumor found primarily in children.
- Ultrasound typically reveals multiple small cysts arising from the testicular hilum, sometimes compressing the normal testicular parenchyma.
- These tumors are universally benign and may be managed by observation, tumor excision, or orchiectomy if extensive.
- Associated genitourinary anomalies, particularly renal agenesis, are common. Therefore, patients with cystic dysplasia of the rete testis should undergo upper tract imaging.

27.14 Epidermoid Cysts

- These are benign tumors of epithelial origin and account for 10–15 % of cases.
- These probably represent a monodermal variant of teratoma.
- Epidermoid cysts are composed entirely of keratin-producing squamous epithelium and are universally benign in children and adults.
- They can often be suspected by their typical appearance on ultrasound of a cyst filled with echogenic layered debris (corresponding to the desquamated keratin) giving an “onion-skin” appearance.
- They may be treated by tumor enucleation with no oncological evaluation or follow-up.
- They are often firm and well-defined, with a central hypoechoic region or mixed internal echogenicity surrounded by an echogenic rim on ultrasonography.
- Following tumor enucleation, these tumors do not require follow-up.

27.15 Testicular Microlithiasis (TM)

- This has been identified as a possible risk factor for the development of testicular cancer.
- TM refers to the presence of microcalcifications, usually diffuse, within the parenchyma of the testis on ultrasound.
- The association with testicular malignancies was suggested by the finding that approximately 25 % of adult testes harboring cancer are found to have TM.
- But the causal relationship behind this finding is unclear.
- TM is found incidentally in approximately 2 % of boys and men undergoing ultrasound either for testicular symptoms or as part of a screening study of asymptomatic males.

- There is still insufficient data to quantify the risk, if any, of testicular cancer in boys or men incidentally found to have TM.
- Studies suggest that TM may be most significant when it occurs in conjunction with other risk factors for testicular cancer, such as men with infertility or a history of contralateral testicular cancer.

27.16 Gonadoblastoma

- While rare, certain disorders of sexual development (DSD) harbor a very significant risk for the development of gonadal tumors.
- Some disorders, such as complete androgen insensitivity syndrome, have an increased risk comparable to that of other patients with testicular maldescent.
- But unique to patients with DSD are the risks of tumor formation in dysgenetic or streak gonads. This risk seems to exist almost exclusively in patients with Y chromatin.
- For example, patients with Turner syndrome and any portion of a Y chromosome in their karyotype have an approximately 12 % risk of tumor development; while patients with traditional Turner syndrome and a 45 XO karyotype are at no significant risk for gonadal tumors.
- Similarly the gonads of patients with pure gonadal dysgenesis and Y chromatin as well as the "streak" gonad of patients with mixed gonadal dysgenesis are at a 15–30 % risk for tumor development.
- The tumors arising in the setting of gonadal dysgenesis are usually gonadoblastomas.
- While gonadoblastomas are benign, they are prone to the development of malignant degeneration and overt malignant behavior is seen in 10 % of cases.
- While most cases of malignancy occur after puberty, there have been cases reported in children as well.
- Prophylactic removal of dysgenetic gonads should be undertaken early in life in patients with at-risk karyotypes.
- Gonadectomy is sufficient treatment for gonadoblastoma.
- If malignant degeneration has occurred, then further therapy may be warranted.
- When malignancies occur, dysgerminoma is the most common histological type.
- These tumors are very radiosensitive and the outlook for these patients is generally favorable.
- These occurs in association with disorders of sexual development (intersex).
- About 80 % of cases involve phenotypic females with intra-abdominal testes or streak gonads.
- The putative gonadoblastoma gene is on the Y chromosome, and the tumor almost always develops in a child with a Y chromosome. The streak gonads in patients with mixed gonadal dysgenesis often develop gonadoblastomas.
- The incidence peaks at puberty, and early gonadectomy is recommended in patients at risk for gonadoblastoma.
- Metastatic spread of a gonadoblastoma occurs in 10 % of patients.
- These tumors may elevate serum levels of beta-human chorionic gonadotropin (beta-HCG).

27.17 Cystic Dysplasia of the Testes

- This is a benign lesion that is often associated with ipsilateral renal agenesis or dysplasia.
- This association, along with a characteristic ultrasonographic appearance (i.e., hypoechoic lesions), permits preoperative diagnosis and possible treatment with testicular-sparing surgery.

27.18 Leukemia and Lymphoma

- These are the most common secondary malignancies to affect the testis.
- These tumors can present bilaterally, and, because the blood-testis barrier protects the intratesticular cells, the testis may be the site

of residual tumor in children after chemotherapy.

- Metastatic disease to the testes should be considered in a child presenting with bilateral testicular tumors.
- Paratesticular structures can give rise to various benign (lipoma, leiomyoma, hemangioma, or fibroma) and malignant tumors; however, these are extremely rare.

27.19 Paratesticular Rhabdomyosarcoma

- This is the most common malignant tumor (17 %) and may arise from the distal spermatic cord and appear as a scrotal mass or hydrocele.
- These tumors have a bimodal distribution and occur in boys aged 3–4 months and in teenagers.
- Up to 70 % of cases involve the retroperitoneal lymph nodes at presentation.
- About 90 % of paratesticular rhabdomyosarcomas demonstrate a favorable embryonal pattern on histology.
- Paratesticular rhabdomyosarcomas usually present with an enlarging painless scrotal mass.
- By the time of presentation distinction from a primary testicular tumor is usually not possible on physical examination, though the extratesticular nature of the tumor is usually apparent on ultrasound
- The initial management for paratesticular rhabdomyosarcomas is an inguinal excision of the tumor and testis.
- The excision should be performed just as for a testicular malignancy.
- Trans-scrotal biopsies of solid scrotal masses should be avoided due to the risk of seeding of the incision if the mass is indeed a rhabdomyosarcoma.
- All children with rhabdomyosarcoma require vincristine, Adriamycin, and dactinomycin (VAC) chemotherapy or treatment with a combination of these drugs. Patients with evidence of metastatic disease may require radiation therapy.
- Routine dissection of the retroperitoneal lymph nodes is recommended in all patients aged 10 years or older (regardless of the imaging results) and in patients younger than 10 years whose images show retroperitoneal disease.
- Children younger than 10 years have a survival rate of nearly 95 %. Children older than 10 years have a worse prognosis and an increased risk for involvement of the retroperitoneal lymph nodes; therefore, an aggressive approach with dissection of the retroperitoneal lymph nodes is recommended.
- Paratesticular rhabdomyosarcoma should be evaluated for metastasis including:
  - CT of the chest, abdomen, and pelvis.
  - The most common sites of metastases are the retroperitoneum and lungs.
- Patients with retroperitoneal metastases undergo a modified unilateral nerve-sparing retroperitoneal lymph node dissection.
- All patients are treated with chemotherapy and those with positive retroperitoneal nodes receive radiation therapy as well.
- Younger children with a normal abdominal CT may be treated with chemotherapy alone without a staging retroperitoneal lymph node dissection.
- The role of staging RPLND in patients with clinical stage 1 disease is based on experience in the Intergroup Rhabdomyosarcoma Studies (IRS).
  - IRS-III (from 1984 to 1991) required a staging unilateral RPLND for all clinical stage 1 patients.
  - In IRS-IV (from 1991 to 1997) patients with a negative CT scan did not undergo staging RPLND (and did not receive radiation to the retroperitoneum).
- This approach resulted in a worrisome decrease in the percentage of patients diagnosed with metastatic disease in IRS-IV, particularly among adolescents.
- Furthermore, adolescents with clinical stage 1 disease in IRS-IV had a 3-year event-free

survival (EFS) of only 68 % compared to a 100 % survival for patients with recognized lymph node involvement (who received radiation and more intense chemotherapy) presumably due to under-staging and under-treatment of those stage 1 patients with occult retroperitoneal disease.

- Such discrepancies were not seen in the prepubertal patients.
- Based on these data, patients over 10 years of age with or without radiographic evidence of retroperitoneal disease should undergo a staging RPLND and receive radiation in addition to chemotherapy if the lymph nodes are positive.
- Younger children with a normal abdominal CT may be treated with chemotherapy alone without a staging RPLND.
- These tumors are highly aggressive and spread via the blood, lymphatics, or direct extension to the lungs, the cortical bone, or to the bone marrow in 20 % of patients at the time of diagnosis.
- Radical inguinal orchiectomy followed by retroperitoneal lymph node dissection is recommended for all children older than 10 years and for those younger than 10 years with retroperitoneal disease.
- Patients with positive lymph nodes are treated with multimodal therapy (chemotherapy and radiation).
- The overall survival rates for patients with paratesticular rhabdomyosarcoma is currently about 90 %.

27.20 Prognosis and Outcome

- In the past, the survival rates from testicular cancer were low.
- Perhaps the greatest advance in the management of testicular cancer was the introduction of platinum-based chemotherapy.
- Survival for both prepubertal and adult tumors has increased dramatically since its introduction.
- Multiagent chemotherapy has become the standard therapy for virtually all metastatic prepubertal testicular malignancies.
- Since the introduction of adjuvant chemotherapy, chiefly platinum-based drugs like cisplatin and carboplatin, the outlook has improved substantially.
- The survival rates have improved markedly and currently the cure rates are over 95 %.
- With recent advances in radiologic staging, serum tumor marker surveillance, and platinum-based chemotherapy for advanced disease, overall survival rates for patients with seminoma have increased to more than 90 %.
- Nearly 100 % of patients with stage I testicular seminoma are cured.

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Splenogonadal Fusion

28

28.1 Introduction

- Splenogonadal fusion is a rare congenital malformation that results from an abnormal fusion between the primitive spleen and gonad.
- Splenogonadal fusion is a rare, benign, congenital anomaly thought to occur between the fifth and eighth weeks of intrauterine life where immature splenic tissue adheres to the developing gonad, epididymis or vas deferens. The splenic tissue is subsequently pulled in a caudal direction with descent of the gonad.
- It was first described in 1883 by Bostroem.
- Since then more than 200 cases of splenogonadal fusion have been described in the literature, most of them are single case reports.
- Its first categorization was made in 1956 by Putschar and Manion.
- Karaman and Gonzales in 1996 reviewed 137 cases of splenogonadal fusion and surprisingly 37 % of the patients had orchiectomy because of suspicion of a testicular tumor.
- This is of great importance and to obviate this physicians caring for these patients should be aware of this and intra-operatively if there is doubt concerning the nature of the swelling, intra-operative frozen section biopsy should be performed to avoid unnecessary orchiectomy.
- Splenogonadal fusion occurs more commonly in males with a male-to-female ratio of 15:1. This figure may of course be inaccurate due to the relative inaccessibility of the ovary to clinical examination.
- It is seen nearly always on the left side.
- Splenogonadal fusion typically presents as an asymptomatic testicular mass.
- Other manifestations may include acute testicular pain and swelling caused by ectopic splenic tissue infections.
- Splenogonadal fusion is a very rare congenital anomaly that must be kept in mind and thought of especially if a child presents with an unusual scrotal swelling.
- It is rarely diagnosed preoperatively.
- If suspected preoperatively, the diagnosis can be confirmed by a ^{99m}Tc-sulphur colloid scan.
- There are two types of splenogonadal fusion, continuous and discontinuous.
- In continuous splenogonadal fusion there remains a connection between the main spleen and gonad.
- In discontinuous splenogonadal fusion, ectopic splenic tissue is attached to the gonad, but there is no connection to the main spleen.
- The continuous form occurs when the normally located spleen is attached to the gonad by a discrete cord.
- In the discontinuous type the splenic tissue is attached to the gonad and completely separated from the normal spleen.
- Both types occur with equal frequency and the discontinuous type may be discovered incidentally during herniotomy or orchidopexy or present as a scrotal swelling. Awareness of this is of great importance to avoid unnecessary orchiectomy mistaken it for a testicular tumor (Fig. 28.1).

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A.H. Al-Salem, *An Illustrated Guide to Pediatric Urology*, DOI 10.1007/978-3-319-44182-5_28

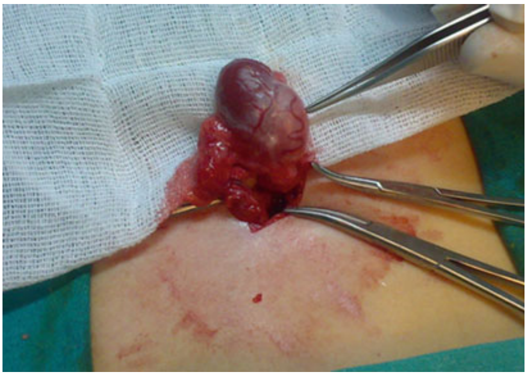

Fig. 28.1 A clinical intraoperative photograph of splenogonadal fusion diagnosed in a child with unusual testicular swelling

- Treatment is surgical excision and every attempt should be made to preserve the gonad at the time of dissection and excision which should not be difficult since true fusion with the gonad is rare.
- Although there have been few reports of an association of testicular neoplasms with splenogonadal fusion, it appears that this is a coincidental finding rather than an association as these tumors occurred in adults with undescended testes.
- The diagnosis of splenogonadal fusion should always be kept in mind and included in the differential diagnosis of testicular swelling in infants and children (Fig. 28.1).

28.2 Etiology

- The exact etiology of splenogonadal fusion is not known.
- Embryologically, the testis starts to descend from its initial embryological position between the dorsal mesogastrium and the mesonephros at around the eighth week of intrauterine life.
- This occurs at the time of splenic development.
- Embryologically, the spleen is formed by a proliferation of mesodermal cells in the dorsal mesogastrium around the fifth and sixth weeks of gestation.
- As a result of normal gastric rotation, the spleen moves in front of the gonadal ridge and mesonephros.
- Splenogonadal fusion is thought to result from partial fusion of splenic and gonadal tissues in the fourth to eighth weeks of intra-uterine life.
- Subsequent descent of the gonad during the eighth to tenth weeks of gestation results in descent of a part of the developing spleen along with it.
- In the discontinuous type, there is complete detachment from the normal spleen while in the continuous type there is attachment to the normal spleen by a cord-like structure.
  - This cord can be made up of splenic tissue or totally fibrotic.
  - Occasionally, there are multiple nodules along this cord which represent foci of splenic tissue that got detached and developed separately. This however does not fully explain the occasional occurrence of right sided Splenogonadal fusion.
- It has been postulated that contact between the gonadal ridge and the primitive spleen precipitated by stress factors (vascular or otherwise) may be responsible for a continuous splenogonadal fusion.
- A more recent hypothesis is based on the capacity of splenic cells to migrate at early stages of development. The spleen is partly responsible for the development of blood cells in the fifth week of gestation. A migration and colonization of splenic cells to its nearby structures namely the gonadal anlage could be responsible for both splenogonadal fusion as well as the explanation for its high association to cryptorchidism.
- It is important to note that the splenic and the testicular tissue of splenogonadal fusion are normal hence orchiectomy or splenectomy is not indicated.

28.3 Classification

- Putschar and Manion in 1956 and in a collective review of 30 cases classified splenogonadal fusion into two types, continuous and discontinuous.
- Splenogonadal fusion is divided into two types:
  - Continuous
  - Discontinuous

- In the continuous type, there is a direct connection between the normal spleen and gonad by a cord that may be:
  - Totally made up of splenic tissue
  - Multiple connected beads of splenic tissue
  - A cord made up of fibrous tissue
- In the discontinuous type there is no connection between the normal spleen and ectopic spleen that is attached to the gonad. This is considered a rare variant of an accessory spleen.
- Both types occur with relatively equal frequency.
- Some authors have suggested that because of the high association of continuous splenogonadal fusion with limb defects, continuous fusion should be regarded as an independent syndrome classified by its associated defects (limb defects, facial or other structures).

28.4 Associated Anomalies

- Splenogonadal fusion is associated to a wide variety of malformations.
- Cryptorchidism and inguinal hernias are the most common malformations associated with splenogonadal fusion.
- In total, 31 % of splenogonadal fusion patients are diagnosed with cryptorchidism or inguinal hernias, and in 59 % of cases the cryptorchidism is bilateral.
- Other malformations include:
  - Limb defects such as peromelia
  - Micrognathia
  - Cleft palate
  - Spinal malformations
  - Cardiac anomalies
  - Microgastria
  - Osteogenesis imperfecta
  - Spina bifida
  - Congenital diaphragmatic hernia
  - Anorectal anomalies
  - Craniosynostosis
  - Moebius syndrome
  - Roberts's syndrome which consists of limb deficiencies, facial anomalies due to premature centromere separation
- Splenogoadal fusion with limb defects has also been associated to the Hanhart anomaly and the femoral facial syndrome.
- In cases of continuous splenogonadal fusion, 50 % are accompanied by other congenital malformations.
- The incidence rate of associated anomalies for continuous splenogonadal fusion is fivefold higher than that of discontinuous splenogonadal fusion and most cases are accompanied by limb defect syndrome. These are called splenogonadal fusion limb defect syndrome (SGFLD).
- The majority (83 %) of splenogonadal fusion limb defect syndrome (SGFLD) are seen in those with continuous splenogonadal fusion and 70 % are associated with micrognathia.
- Approximately one-fifth of continuous splenogonadal fusion patients also have other major congenital defects, such as limb hypoplasia, micrognathia, cardiac defects, palatal defects and anal defects.

28.5 Clinical Features

- Splenogonadal fusion is commonly asymptomatic discovered incidentally during routine herniotomy or orchidopexy.
- Many of these cases however go passed unnoticed or discovered at autopsy.
- In the pediatric age group, these patients commonly present with a scrotal swelling and may rarely present with an acute scrotal pain as a result of torsion or involvement of splenic tissue with other pathological conditions such as mumps, malaria, leukemia, trauma and infectious mononucleosis.
- The left side is far more commonly affected than the right in 98 % of the cases.
- It is more common in males with an M: F of 15:1. This however may not be true as the ovary is not easily accessible and since the majority of these cases are asymptomatic, the incidence of splenogonadal fusion in females may be underestimated.
- Not uncommonly splenogonadal fusion is associated with other anomalies or discovered during the evaluation of these associated anomalies. This is more so with the continuous type which is known to be associated with other associated anomalies in as much as 33 % of the cases.

- One of the most common forms of presentation of splenogonadal fusion is testicular swelling.
- This swelling might appear as a hydrocele if it is painless.
- The swelling may be accompanied by pain in cases where the ectopic splenic tissue is affected by systemic disease, like Malaria, or mumps.
- Splenogonadal fusion is commonly diagnosed in children and adolescents.
  - The number of cases reported in patients <10 years of age account for 50 % of the total cases reported.
  - The number of cases reported in patients <20 years old account for 70 %.
- Patients most commonly present under the age of 20 years with:
  - Cryptorchidism
  - Left inguinal hernia
  - A left scrotal mass
- Splenogonadal fusion may be an incidental finding during an orchidopexy and in these patients it is important to recognize this and manage the patient accordingly.
- The presentation may, however, be due to the complications of the splenogonadal fusion including:
  - Intestinal obstruction
  - Acute painful scrotal splenic enlargement
  - Rupture
- One-third of cases are associated with other congenital abnormalities including limb and orofacial malformation.
- These associated anomalies are more likely seen in the continuous form.
- There is also an association between splenogonadal fusion and testicular malignancy.
  - In the literature, there are about seven reported cases of splenogonadal fusion and testicular malignancy but in all of these cases the malignancy developed in adults with undescended testes or following orchidopexy for undescended testes.
  - This may represents an association rather than an increased risk in this subset group of patients as patients with undescended testes have a well-known increased risk of malignancy.

28.6 Investigations

- Splenogonadal fusion remains a diagnostic challenge and rarely it is diagnosed preoperatively.
- The diagnosis of splenogonadal fusion should always be kept in mind and included in the differential diagnosis of testicular swelling in infants and children.
- Physicians caring for these patients should be aware of this and preoperative consideration of the diagnosis may help avoid unnecessary orchiectomy.
- The radiologic identification of splenogonadal fusion is important to prevent unnecessary orchiectomy due to its macroscopic resemblance to cancer.
- Imaging modalities including ultrasonography, computed tomography (CT), magnetic resonance imaging (MRI) and 99TCm spleen scanning, aid with the diagnosis of splenogonadal fusion.
- Recently, laparoscopy is used to diagnose and manage patients with suspected splenogonadal fusion.
- Scrotal ultrasound may show ectopic splenic tissue as an encapsulated homogeneous extra testicular mass, isoechoic with the normal testis.
- The presence of splenic tissue may be confirmed with a technetium-99m sulfur colloid scan.
- Often, the definitive diagnosis is made postoperatively by histology and orchiectomy is not necessary as the splenic tissue can be dissected off the testicle.
- The goal should be to preserve the testis and the use of frozen section may be useful in distinguishing between splenogonadal fusion and primary testicular and para-testicular neoplasms.

28.7 Treatment

- Preoperative diagnosis of splenogonadal fusion is uncommon.
- Intraoperatively, the diagnosis may also be difficult and it not uncommon for this to be confused with a testicular tumor.

- Several patients with splenogonadal fusion have undergone unnecessary orchiectomy due to the misdiagnosis of a testicular tumor.
- Spleen tissue is easily separated from the gonad and as a result the testis may be saved and retained.
- If the diagnosis is not clear and a tumor is suspected, biopsy and frozen section may aid with the diagnosis.
- Laparoscopy is a safe and reliable approach that is highly accurate in the diagnosis and treatment of nonpalpable testis.

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Acute Scrotum

29

29.1 Introduction

- The term acute scrotum refers to acute scrotal pain with or without swelling and erythema.
- Acute scrotum is considered a surgical emergency and although there are several causes for acute scrotum, prompt differentiation between testicular torsion and other causes of acute scrotum is critical.
- The possibility of testicular torsion and permanent ischemic damage to the testis must always be kept in mind if the diagnosis is delayed.
- There are several causes of acute scrotum and the etiology is age dependent.
- Testicular torsion is commonly seen in neonates and adolescents.
- Torsion of the appendix testis and acute epididymo-orchitis on the other hand are seen most commonly in prepubertal boys.
- The differential diagnosis of acute scrotum include:
  - Testicular torsion (16 %)
  - Torsion of a testicular appendage (46 %)
  - Acute epididymo-orcitis (35 %)
  - Idiopathic scrotal edema
  - Schönlein-Henoch purpura
  - Incarcerated inguinal hernia
  - Scrotal trauma
  - Splenogonadal fusion

Common Causes of Acute Scrotum

1. Testicular torsion (16 %)
2. Torsion of a testicular appendage (46 %)
3. Acute epididymo-orchitis (35 %)
4. Idiopathic scrotal edema
5. Schonlein-henoch purpura
6. Incarcerated inguinal hernia
7. Scrotal and testicular trauma

- The child with acute scrotum should be evaluated rapidly both clinically and if required radiologically and the possibility of torsion of testis must always be kept in mind.
- This is important because salvaging a testis in a child with testicular torsion is time dependent.
- In doubtful cases, it is important to do an emergency testicular exploration rather than wait and loss the testis.

29.2 Torsion of Testes

29.2.1 Introduction

- Testicular torsion is the most surgical emergency of acute scrotum as delay in diagnosis is known to be associated with testicular ischemia and infarction.

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- It results from twisting of the spermatic cord leading to venous and arterial obstruction and loss of the blood supply to the affected testis.
- Early diagnosis and treatment are vital to saving the testis and preserving future fertility.
- Testicular torsion is primarily a disease of adolescents and neonates.
- Neonates develop a special type of testicular torsion which is called intrauterine testicular torsion.
- This is different from the more common torsion seen in adolescent.
  - This type of torsion occurs extravaginally while the adolescent torsion occurs intravaginally.
  - This type of torsion commonly occurs in utero but there are reported cases occurring shortly after birth.
  - Intrauterine torsion is known to be associated with a high incidence of testicular infarction as in the majority of reported cases, the testis is already necrotic at the time of exploration
  - There are however rare reports of testicular salvage in some of these patients.
- Diagnosis of testicular torsion is clinical, and diagnostic testing should not delay treatment.
- Approximately 32 % of pediatric torsion cases resulted in the orchiectomy.

29.2.2 Classification

Testicular torsion is divided into two types (Fig. 29.1):

1. Intravaginal torsion:
   - Intravaginal torsion most commonly occurs in adolescents.
   - Intravaginal torsion constitutes approximately 16 % of cases in patients presenting to an emergency department with acute scrotum.
   - This form of testicular torsion is most commonly seen in males younger than 30 years.
   - The peak incidence occurs at age 12–18 years.
   - The left testis is more frequently involved.
   - Bilateral torsion account for 2 % of all torsions.

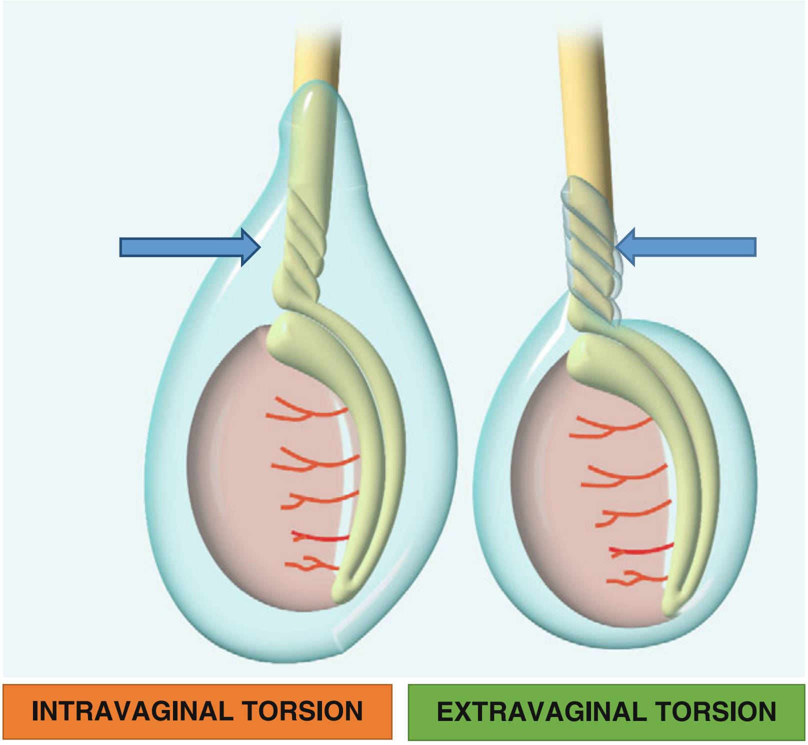
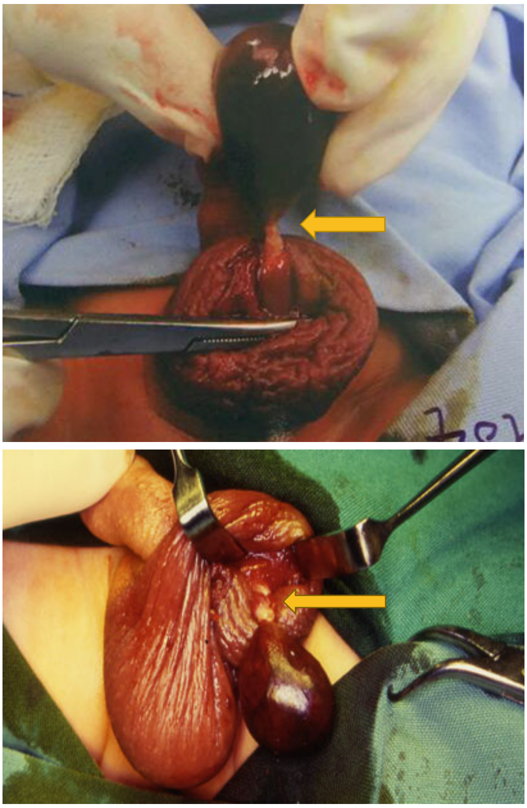


Fig. 29.1 Diagrammatic representation of the two types of testicular torsion

2. Extravaginal torsion (Figs. 29.2 and 29.3):
   - Extravaginal torsion occurs most commonly in neonates.
   - It accounts for approximately 5 % of all torsions.
   - The timing of occurrence of extravaginal torsion is not known exactly and it is estimated that about 70 % of the cases occur prenatally and 30 % occur postnatally.
   - Extravaginal torsion is also known to occur in patients with high birth weight.
   - Extravaginal torsion occurs most commonly on one side and bilateral perinatal torsion is extremely rare, but an increase in the number of case reports with bilateral intrauterine torsion has been observed.
   - The occurrence of bilateral torsion can be:
     - Synchronous (occurring simultaneously)
     - Metachronous (occurring at different times).
     - This is one reasons why contralateral orchidopexy is important in those with unilateral intrauterine torsion.



Figs. 29.2 and 29.3 Intraoperative photographs of two newborns with extravaginal testicular torsion

29.2.3 Etiology

1. Intravaginal torsion:
   - The exact etiology of intravaginal torsion is not known.
   - Normally, once the testes reaches the scrotum it is fixed in place by mature attachments. This ensures firm fixation of the epididymal-testicular complex posteriorly and effectively prevents twisting of the spermatic cord.
   - The tunica vaginalis is normally attached to the postero-lateral aspect of the testes.
   - The most accepted embryological etiology of intravaginal testicular torsion is the bell clapper deformity.
   - This defect occurs in about 17 % of males and is bilateral in 40 %.
   - High abnormal attachment of the tunica vaginalis to the testicle makes the spermatic cord liable to rotate within it, which can lead to intravaginal torsion.
   - In intravaginal torsion, the testis can rotate freely on the spermatic cord within the tunica vaginalis.
   - In males with the bell-clapper deformity, torsion can occur because of a lack of fixation, resulting in the testes being freely suspended within the tunica vaginalis (Fig. 29.4).
   - The bell clapper deformity can result in the long axis of the testicle being oriented transversely rather than cephalocaudal.
   - Another abnormality that can predispose to intravaginal torsion is abnormal mesentery between the testis and its blood supply.

1. Extravaginal torsion:
   - This occurs because the tunica vaginalis is not yet secured to the gubernaculum and, therefore, the spermatic cord, as well as the tunica vaginalis, undergo torsion as a unit.

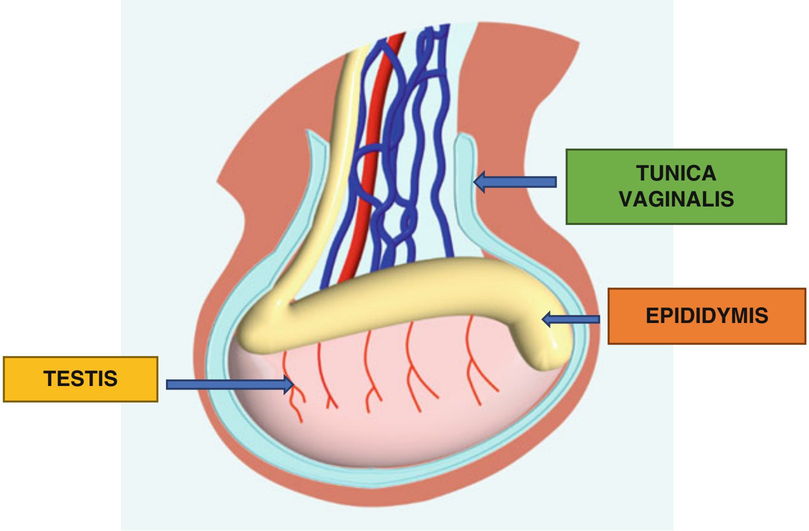


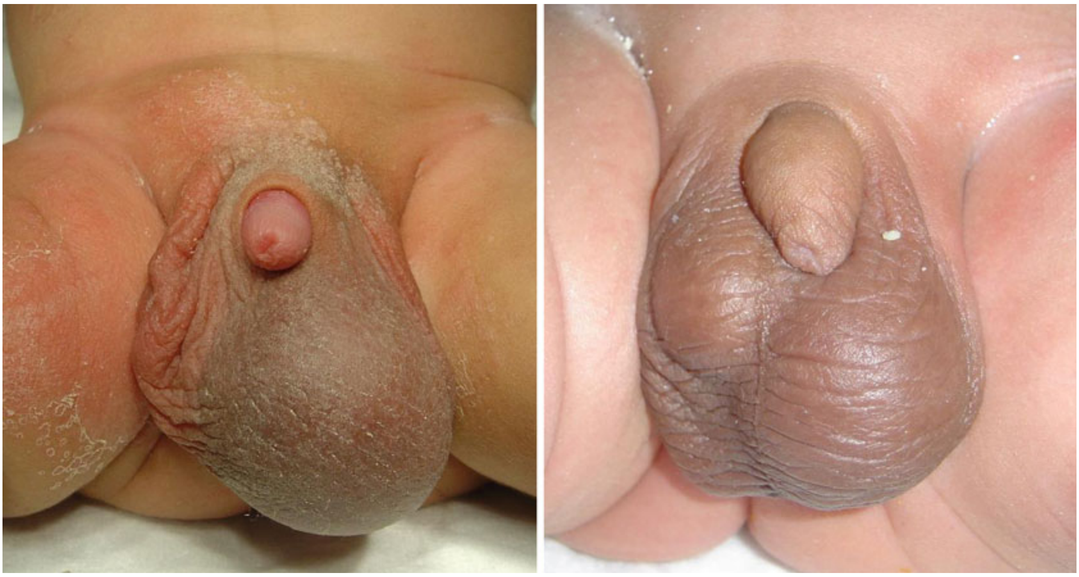
Fig. 29.4 Diagrammatic representation of the bell-clapper deformity. This predisposes to intravaginal torsion of testis

- In neonates, the testes frequently has not yet fully descended into the scrotum, where it becomes attached within the tunica vaginalis. This mobility of the testicle predisposes it to extravaginal torsion.

29.2.4 Clinical Features

Intravaginal Torsion

- The usual presentation of intravaginal testicular torsion is a sudden onset of severe unilateral scrotal pain followed by inguinal and/or scrotal swelling. Gradual onset of pain is an uncommon presentation.
- The pain may decrease in severity as the necrosis of testis becomes more complete.
- Torsion of testis commonly occurs spontaneously but may occur during sports or physical activity.
- Torsion of testis can also occur in association of trauma. This is seen in 4–8 % of the cases.
- Approximately one third of patients also have gastrointestinal upset with nausea and vomiting.
- The patients rarely report voiding difficulties or painful micturition.
- In some patients, scrotal trauma or other scrotal disease (including torsion of appendix testis or epididymitis) may precede the occurrence of subsequent testicular torsion.
- The patients may describe previous episodes of recurrent acute scrotal pain that has resolved spontaneously. This history is highly suggestive of intermittent torsion and detorsion of the testis. A detailed history is important in this regard.
- Acute testicular torsion develops in 10 % of patients with intermittent torsion while they waite for surgery.
- Physical examination may reveal:
  - A swollen, tender, high-riding testis
  - Abnormal transverse lie of testis
  - Loss of the cremasteric reflex
  - Edema involving the entire scrotum
  - Enlargement and edema of the testis
  - Fever is uncommon
  - Scrotal erythema
- The cremasteric reflex is almost always absent or diminished on the affected side in patients with testicular torsion.
- Prehn’s sign: Relief of pain with elevation of the affected testis.
- Although a negative Prehn’s sign is classically thought to be a predictor of torsion, this is unreliable for diagnosis.
- Factors predictive of testicular torsion include:
  - Acute onset of testicular pain
  - Duration of pain of less than 6 h
  - Fever, nausea and vomiting
  - History of trauma or physical activities



Figs. 29.5 and 29.6 Clinical photographs showing two newborns with torsion of testis. Note the enlarged scrotum in both. Sometimes the skin is discolored and the affected testis is elevated

  - Absence of cremasteric reflex
  - Abnormal transverse lie of affected testis

Extravaginal Torsion

- In neonates, prenatal extravaginal torsion presents as a hard, nontender testis that is fixed to the overlying scrotal skin which is discolored (Figs. 29.5 and 29.6).
- The affected testis is swollen.
- Unilateral absence of the testis with blind-ending vas and vessels is thought to be a manifestation of early in utero torsion. This is also supported by finding hemosiderin in the distal section of the spermatic cord (Fig. 29.7).
- Acute scrotal swelling and tenderness without fixation to the scrotal wall, may represent a postnatal torsion with some hope of subsequent testicular salvage with early surgical management.
- Prenatal torsion manifests as:
  - A firm, hard, scrotal mass
  - It does not transilluminate
  - It occurs in an otherwise asymptomatic, healthy and of good weight male newborn
  - The scrotal skin characteristically fixes to the necrotic gonad and the scrotum is enlarged

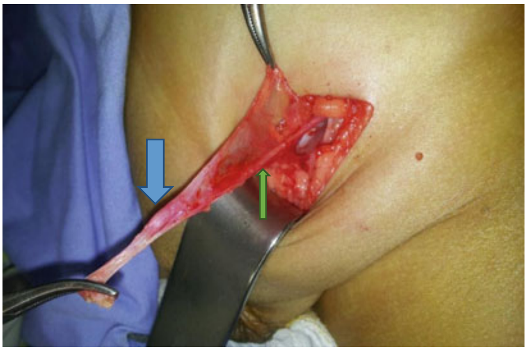


Fig. 29.7 A clinical intraoperative photograph showing a small atrophic testis with an intact vas suggestive of intrauterine torsion of testis

29.2.5 Effects of Torsion of Testes

- Torsion of the testes causes venous occlusion and engorgement as well as arterial ischemia and subsequent infarction of the testis. The extent of this depends on two factors:
  - The degree of torsion (Fig. 29.8):
- Torsion occurs as the testis rotates between 90° and 180°, compromising blood flow to and from the testis.
- Incomplete or partial torsion occurs with lesser degrees of rotation.

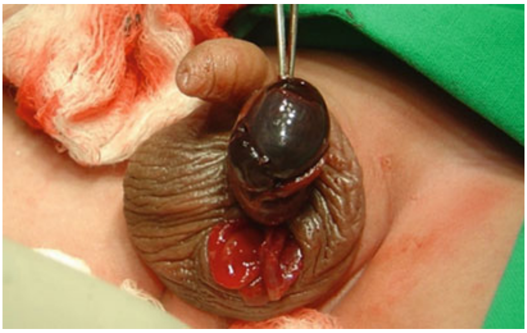


Fig. 29.8 A clinical photograph showing a newborn with extravaginal torsion. Not the already necrotic testis

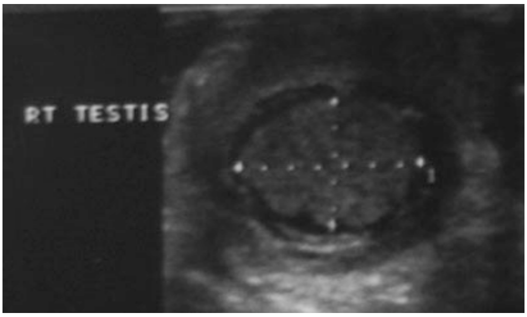


Fig. 29.9 A Doppler ultrasound showing torsion of the right testis

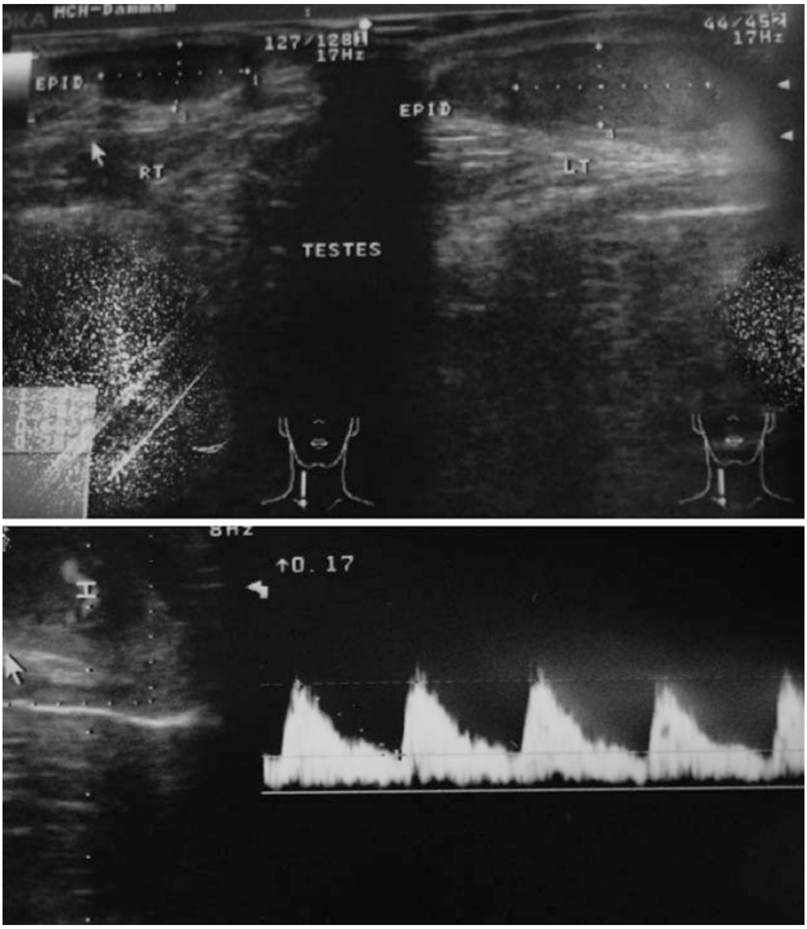
- Complete torsion usually occurs when the testis twists 360° or more. The degree of torsion may extend to 720°.
  - The duration of torsion:
    - The duration of torsion is the most important factor that influences the rates of both immediate salvage and late testicular atrophy.
    - Testicular salvage is most likely if the duration of torsion is less than 6 h.
    - If 24 h or more elapse, testicular necrosis develops in most patients.
- The cause of decreased fertility observed in patients with unilateral testicular torsion is not known and two factors were suggested as possible theories.
  - An inherent bilateral testicular abnormalities
  - An autoimmune mechanism affecting the contralateral testis. This hypothesis however was not supported.

29.2.6 Investigations

- Testicular torsion is a clinical diagnosis.
- If the history and physical examination strongly suggest testicular torsion, the patient should undergo emergency exploration without delay to perform investigations and imaging studies.
- When a low suspicion of testicular torsion exists, color Doppler ultrasonography can be used to demonstrate arterial blood flow to the testis and provide information about other testicular pathology (Fig. 29.9).
- The sensitivity of color Doppler examination in detecting acute testicular torsion in children is 90–100 %, with specificity being 100 % (Figs. 29.10 and 29.11).
- Other studies have suggested that color Doppler ultrasonography was only 86 % sensitive, 100 % specific, and 97 % accurate in the diagnosis of testicular torsion.
- If the diagnosis is equivocal, radionuclide scan of the testis can be helpful to assess blood flow and to differentiate testicular torsion from other causes of acute scrotum.
- Radionuclide scans have a sensitivity of 90–100 % in detecting testicular blood flow.
- If the patient does not show clinical evidence of testicular torsion, a urinalysis and culture may help exclude urinary tract infection and epididymitis.
- The complete blood count can be normal. However, the WBC count is elevated in as many as 60 % of patients who have testicular torsion.

29.2.7 Treatment

- Surgical exploration and testicular detorsion is the definitive treatment for testicular torsion.
- Manual nonsurgical detorsion of the affected testis may be attempted but is usually difficult because of acute testicular pain during manipulation. During this maneuver, the testis should be detorted in medial to lateral direction.



Figs. 29.10 and 29.11 A Doppler ultrasound showing epididymitis. Note the enlarged left epididymis and the good blood flow to the testis

- If manual detorsion is successful based on complete resolution of symptoms and confirmed by color Doppler ultrasound in a patient with testicular torsion, the patient should undergo definitive surgical fixation of both testes before leaving the hospital. The operation can be performed as an urgent rather than an emergency procedure.
- A bilateral scrotal orchidopexy is recommended to treat torsion of testis. This is to prevent torsion of the other testis.
- The treatment of neonatal torsion is still controversial.
  - Some advocate elective rather than emergency exploration and contralateral orchidopexy because bilateral (synchronous or asynchronous) neonatal testicular torsion has been described.
  - If the testis is necrotic, an orchiectomy and contralateral orchidopexy is performed.
  - Retention of a necrotic testis may exacerbate the potential for subfertility, presumably because of development of an autoimmune phenomenon. This however is not fully supported.
  - There are others who advocate emergency exploration.
    - The argument in favor of this is that the timing of testicular torsion is not exactly known and although the chance of saving the testis is small, this is worth doing.
    - Add to this the fact that these patients are usually healthy with no other abnormalities and of good size and currently the anesthesia is safe (Figs. 29.12, 29.13, 29.14 and 29.15).
- The placement of a testicular prosthesis is usually delayed for 6 months, until healing is complete and inflammatory changes resolve.

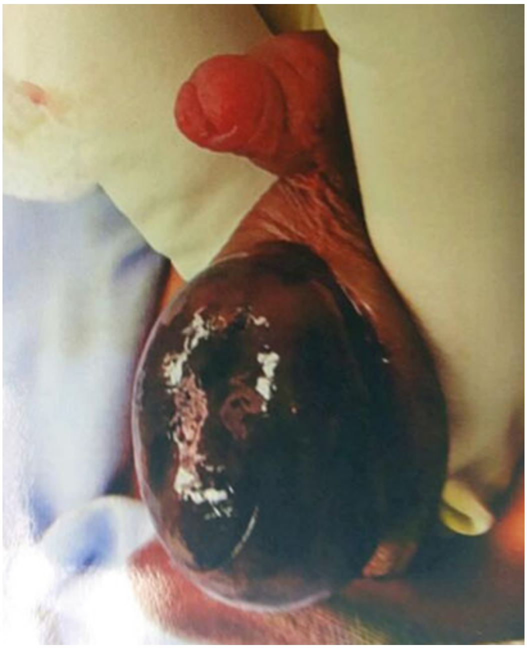


Fig. 29.12 An intraoperative photograph showing an already necrotic testis in a newborn with testicular torsion

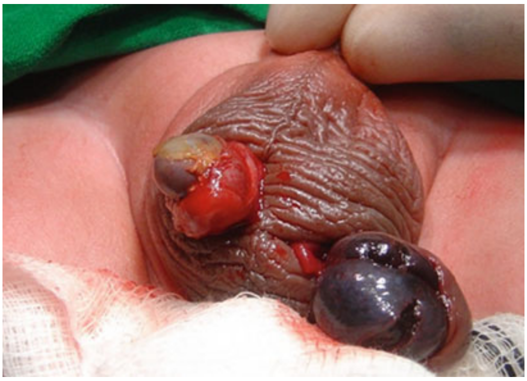
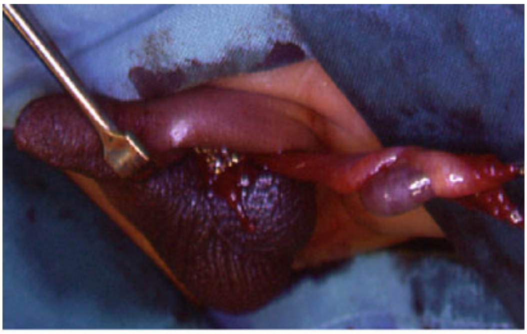


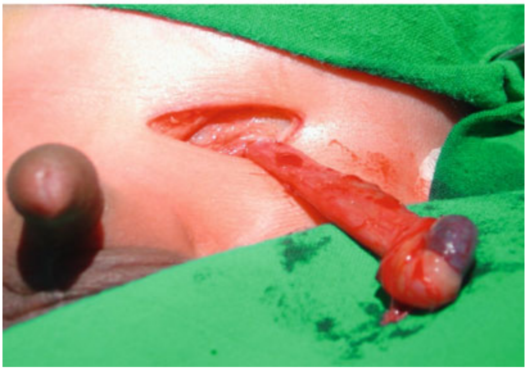
Fig. 29.13 An intraoperative photograph showing already necrotic testes in a newborn with bilateral intrauterine testicular torsion

29.3 Torsion of the Testicular or Epididymal Appendage

29.3.1 Introduction

- Torsion of testicular appendices is one of the most common causes of acute scrotum (Fig. 29.16).





Figs. 29.14 and 29.15 Intraoperative photographs showing viable testes in two newborns with intrauterine torsion following exploration and detorsion of the testes

- There are two types of testicular appendices:
  - The appendix testis
  - The epididymal appendix
- Torsion of testicular appendices is considered the leading cause of acute scrotum in children.
- In those with acute scrotal pain, the incidence of torsion of testicular appendage ranges from 46 % to 71 %.
- Torsion of the testicular appendices is virtually a benign condition, but must be distinguished from testicular torsion.
- The appendix testis and epididymal appendix are commonly pedunculated and because of this are predisposed to torsion.
- Torsion of either appendage (The appendix testis and epididymal appendix) produces pain similar to that experienced with testicular torsion, but the onset is usually more gradual.

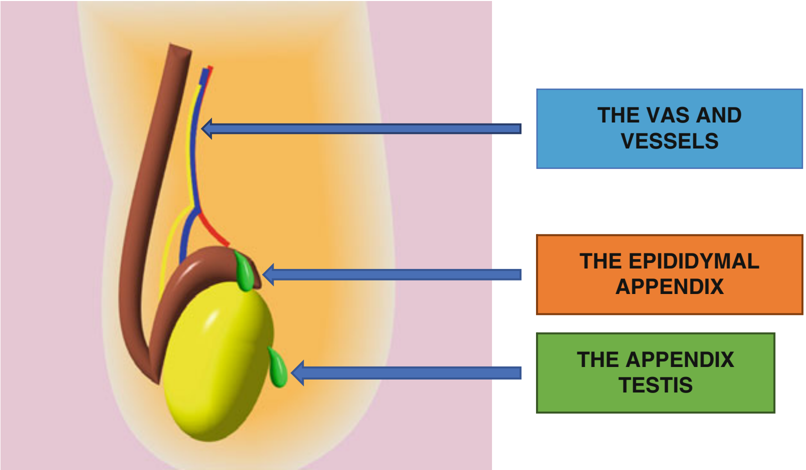


Fig. 29.16 Diagrammatic representation of the two common testicular appendages

29.3.2 Embryology

- The appendix testis:
  - This is a Müllerian duct remnant.
  - It is present in 92 % of all testes.
  - It is located at the superior pole of the testis in the groove between the testis and epididymis.
  - It is the most common appendage to undergo torsion.
- The epididymal appendix:
  - This is a Wolffian duct remnant.
  - The appendix epididymis is present in 23 % of testes.
  - It is usually located on the head of the epididymis.
  - It is the second common appendage to undergo torsion.

29.3.3 Clinical Features

- The majority (80 %) of torsion of the testicular or epididymal appendage occurs in boys aged 7–14 years (Mean age 10.6 years).
- The usual presentation is acute scrotal pain but the onset is more gradual. This is important in distinguishing this from testicular torsion which presents with sudden acute scrotal pain.
- The pain is more localized to the upper pole of the testis which is also tender.

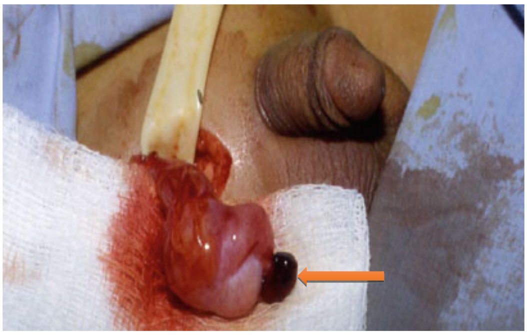


Fig. 29.17 An intraoperative photograph showing torsion of the appendix testis

- The pain is usually not associated with systemic symptoms such as nausea, vomiting or urinary symptoms.
- Usually, the scrotum appears normal but sometimes there is an associated erythema and edema.
- The cremasteric reflex is usually intact.
- Occasionally, a paratesticular nodule at the superior aspect of the testicle is present. This is called the blue-dot sign which is present in only 20 % of cases (Fig. 29.17).

29.3.4 Investigations and Treatment

- Ultrasonography can be useful in distinguishing torsion of a testis and torsion of an appendix testis.

- Color Doppler ultrasonography is the imaging modality of choice for evaluation of the acute scrotum.
- This usually shows normal blood flow to the testis and sometimes an increase blood flow on the affected side due to inflammation.
- This is a self- limiting condition and most cases are treated conservatively.
- Rarely surgery is indicated:
  - If it is difficult to differentiate from testicular torsion.
  - If the pain is severe and cannot be controlled by analgesics.
- The management includes:
  - Bed rest and scrotal elevation.
  - Nonsteroidal anti-inflammatory drugs and analgesics.
  - Torsion of a testicular appendage may be misdiagnosed as epididymitis but if the urinalysis is normal, no antibiotic therapy is required.
  - The inflammation usually resolves within a week.

29.4 Epididymitis, Orchitis, and Epididymo-orchitis

29.4.1 Introduction

- Acute epididymo-orchitis is a clinical diagnosis consisting of pain, swelling and inflammation of the epididymis, with or without inflammation of the testes.
- It is an important cause of acute scrotum in children (Fig. 29.18).
- Orchitis (infection limited to the testis) is much less common and commonly caused by mumps.
- Chronic epididymitis refers to inflammation that lasts for more than 6 months.
- Epididymitis is considered the most common cause of acute scrotum in older boys, and it is important to differentiate this from testicular torsion.
- There is an increased incidence of genitourinary abnormalities in prepubertal boys with epididymitis.

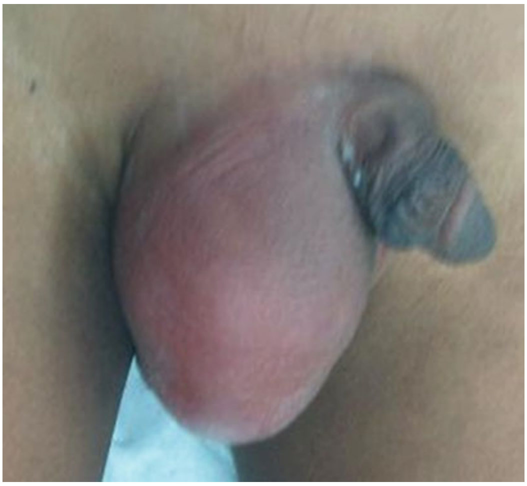


Fig. 29.18 A clinical photograph showing a child with acute scrotum secondary to severe epididymo-orchitis with intrascrotal abscess formation

- It has been shown that 47 % of prepubertal boys and 75 % of infants with epididymitis have an underlying urogenital anomaly.

29.4.2 Etiology

- The exact etiology of acute epididymitis is unknown.
- Acute epididymitis is believed to be caused by the retrograde passage of urine from the prostatic urethra to the epididymis via the ejaculatory ducts and vas deferens.
- There are however several contributing causes for acute epididymitis including:
  - Genitourinary abnormalities in infants and young boys.
  - In older boys, acute epididymitis is often idiopathic.
  - Epididymitis can also be secondary to systemic diseases, such as:
    - Sarcoidosis.
    - Kawasaki disease.
    - Henoch-Schönlein purpura.
  - Inflammation of the epididymis may be also reactive secondary to trauma or torsion of an appendix testis.
  - Chemical irritation from sterile reflux of urine into the seminal tract.

  - Epididymitis in children can also be drug-induced (amiodarone-induced epididymitis)
- Bacterial epididymitis is caused by several organisms including:
  - Coliforms, Pseudomonas species, Ureaplasma, Mycoplasma species, Staphylococcus, Proteus species, and Haemophilus influenzae.
  - In sexually active patients, Chlamydia and/or Neisseria gonorrhoeae may be the causative organism.
  - Viral causes include paramyxovirus, Coxsackie virus, echovirus, and adenovirus.
  - Granulomatous epididymitis is very rare in children and can be secondary to tuberculosis.

29.4.3 Clinical Features

- The usual presentation is with unilateral scrotal pain and swelling of relatively acute onset.
- Acute epididymitis is usually unilateral but it is bilateral in 5–10 % of the patients.
- There may be a history of a urinary tract infection.
- Tenderness on the affected side.
- The epididymis will be enlarged and tender or the whole testis and epididymis will be tender.
- There may also be erythema and/or edema of the scrotum on the affected side.

29.4.4 Investigations and Treatment

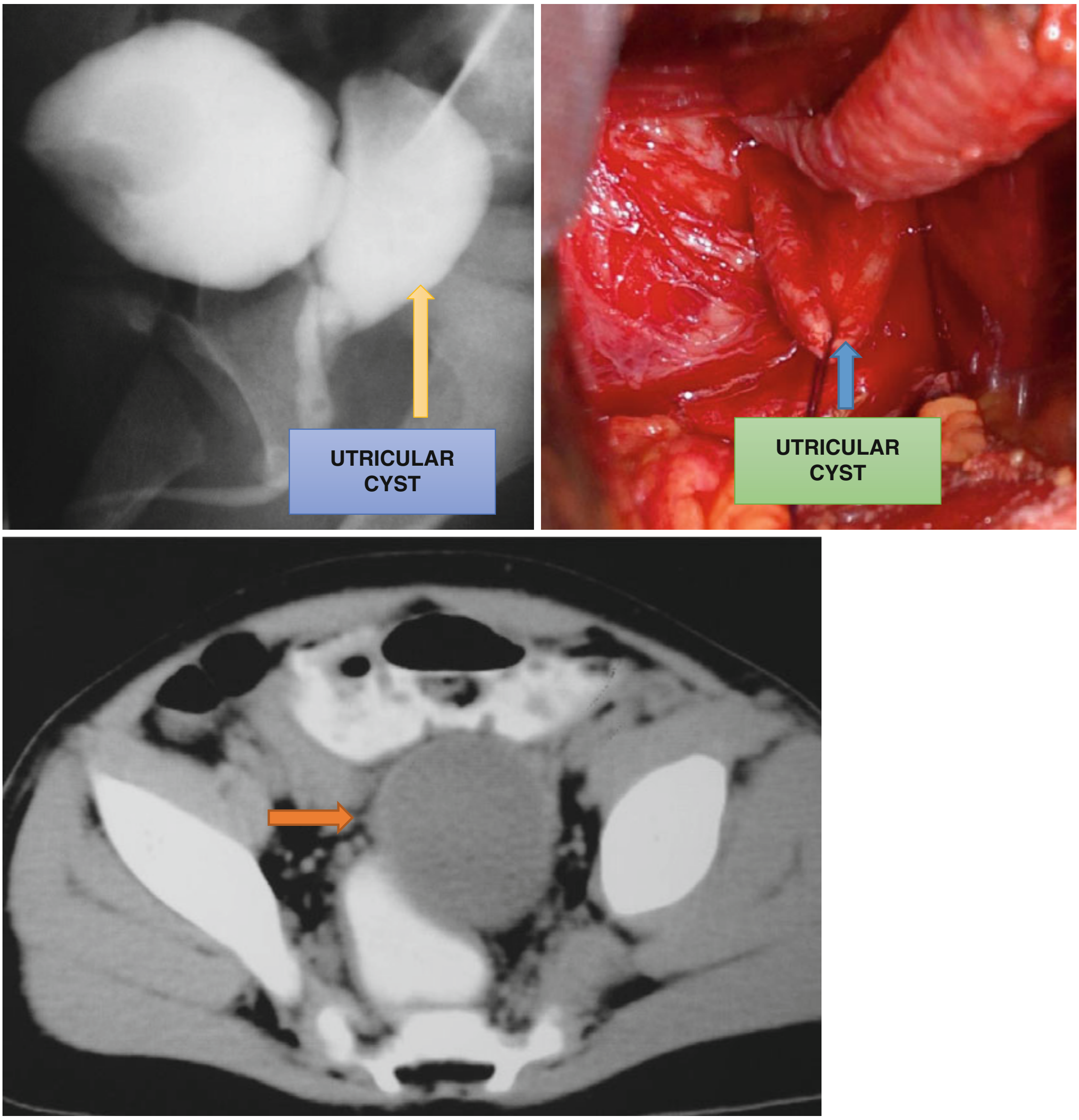
- Urinalysis with culture and sensitivity.
- Blood culture.
- Infants and children with epididymitis have a high incidence of associated urogenital abnormalities, and thus require full urological evaluation.
- Renal ultrasound, a voiding cystourethrogram and urodynamic studies are necessary investigations in prepubertal boys with acute epididymitis. This is specially so in the presence of urinary tract infection (Figs. 29.19, 29.20 and 29.21).

Clinical features	
Pain	96 %
Swelling	100 %
Erythema	72 %
Fever	40 %
Leucocytosis	44 %
A positive urinalysis	24 %
Lower urinary tract symptoms (frquency, urgency, enuresis)	16 %
Nausea and vomiting	16 %

- In patients with signs of urinary tract infection, treatment includes empiric antibiotic therapy until the results of a urine culture are known.
- Treatment should start with an oral or I.V broad-spectrum antibiotic depending on the presence or absence of signs of systemic infection. Treatment should be continued for 10–14 days and the antibiotics modified according to the culture result.
- Patients with underlying genito-urinary abnormalities usually require surgical intervention.
- In the absence of urinary tract infection, treatment is supportive including:
  - Bed rest and scrotal elevation.
  - Non-steroidal anti-inflammatory drugs and analgesics.

Differential diagnosis and management of the acute scrotum

Type	Onset of symptoms	Age at diagnosis	Site of tenderness	Urinalysis	Cremasteric reflex	Treatment
Testicular torsion	Acute	Early puberty	Diffused	Negative	Negative	Surgical exploration
Appendicealr torsion	Subacute	Prepubertal	Localized to upper pole	Negative	Positive	Bed rest and scrotal elevation
Epididymitis	Insidious	Adolescence	Epididymal	Positive or negative	Positive	Antibiotics



Figs. 29.19, 29.20, and 29.21 A micturating cystourethrogram, CT-scan and an intraoperative photograph showing a large utricular cyst in a child with recurrent epididymitis

29.5 Idiopathic Scrotal Edema

- Acute idiopathic scrotal edema is one of the differential diagnosis in children presenting with an acute scrotum.
- Acute idiopathic scrotal edema was first reported by Qvist in 1956.
- It is characterized by scrotal edema and erythema.
- It is a self-limiting condition.
- In idiopathic scrotal edema (Fig. 29.22):
  - The scrotal skin is thickened, edematous, and often inflamed.
  - The testis and epididymis are not tender and of normal size and position.
  - The affected scrotum is enlarged when compared to the other side.
- It occurs less frequently than epididymitis, testicular torsion, or torsion of testicular appendages and is more common in boys than in adults.

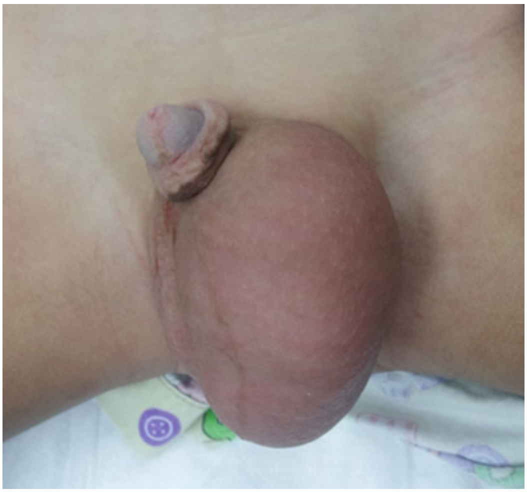


Fig. 29.22 A clinical photograph with idiopathic scrotal edema

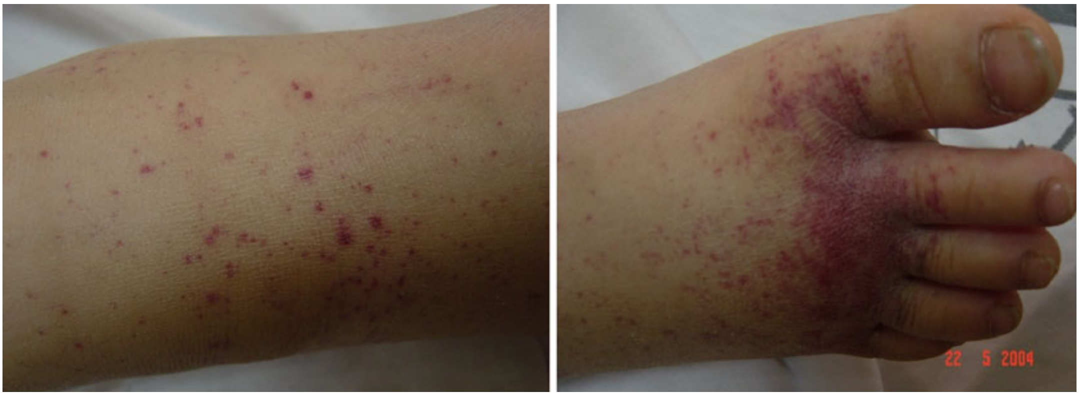
- Over 75 % of cases occur in boys less than 10 years of age.
- Two thirds of cases are unilateral.
- Idiopathic scrotal edema is characterized by:
  - The rapid onset of significant edema without tenderness.
  - Painless erythema and induration of the scrotum.
  - Edema and erythema may extend to the phallus, groin, and lower abdomen.
  - The patient is usually afebrile.
  - Patients may complain of pruritus.
  - All diagnostic tests are negative.
- The etiology of this condition remains unclear.
- An allergic reaction is the most likely cause.
- Sonography plays an important role in excluding testicular torsion, epididymitis, and torsion of a testicular appendage and confirming the diagnosis of acute idiopathic scrotal edema.
- Treatment consists of bed rest and scrotal elevation.
- Analgesics are rarely needed.
- Most cases resolve spontaneously within a few days and do not require specific treatment.
- There is a 20 % recurrence rate.

29.6 Testicular Trauma

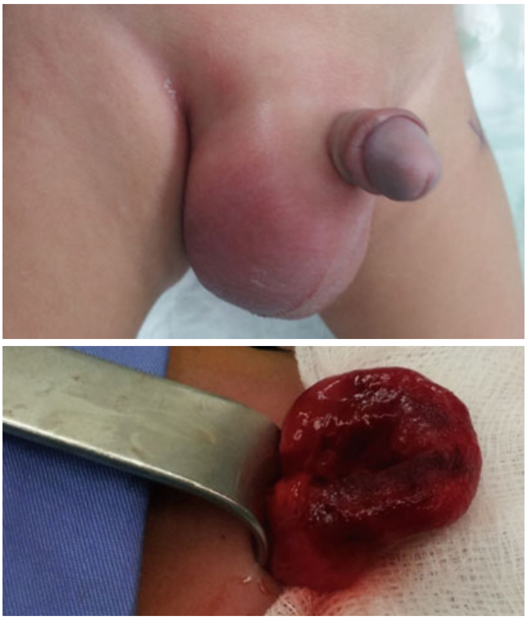
- Testicular injury is uncommon and usually results from either a direct blow to the scrotum or a straddle injury.
- Traumatic damage to the testes results mostly from forceful compression of the testis against the pubic bones.
- Scrotal trauma can also result in intratesticular hematoma, hematocele or laceration of the tunica albuginea (testicular rupture).
- Color Doppler ultrasonography is the imaging technique of choice.
- Testicular rupture requires immediate surgery and repair.

29.7 Other Causes of Acute Scrotum

- Schönlein-Henoch purpura:
  - A systemic vasculitis of unknown etiology.
  - It is characterized by (Figs. 29.23 and 29.24):
- Nonthrombocytopenic purpura
- Arthralgia
- Renal disease
- Abdominal pain
- Gastrointestinal bleeding
- Scrotal pain
  - The onset can be acute or insidious.
  - Hematuria may be present.
  - The syndrome has no specific treatment.
- Incarcerated inguinal hernia:
  - This should be suspected in a child who has a history of intermittent groin swelling.
  - The usual presentation is with an irreducible painful and tender inguinal or inguinoscrotal swelling.
  - In those with strangulated hernia, there may be an associated scrotal swelling and redness (Figs. 29.25 and 29.26).
  - This may be due to bowel congestion and ischemia or sometimes localized bowel perforation.
  - An incarcerated or strangulated hernia requires urgent surgical intervention.



Figs. 29.23 and 29.24 Clinical photographs showing a child with Schönlein-Henoch purpura. Note the skin rash which is nonthrombocytopenic. This patient also had scrotal pain as well as abdominal pain

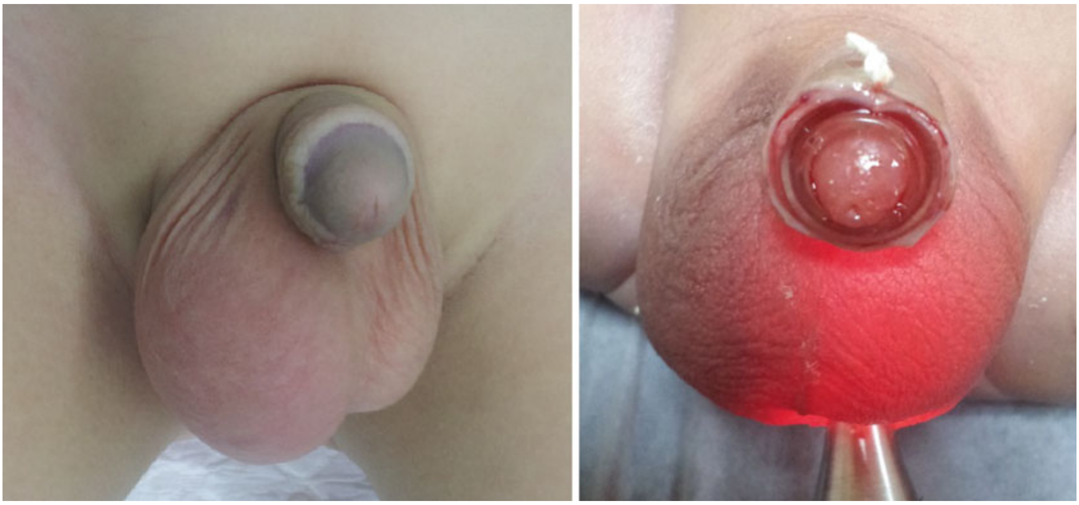


Figs. 29.25 and 29.26 A clinical and intraoperative photographs of a child who presented with a strangulated right inguinal hernia. Note the associated scrotal swelling, and redness secondary to intestinal ischemia

- Hydrocele:
  - A hydrocele occurs because of a patent processus vaginalis.
  - Most hydroceles resolve spontaneously.
  - The usual presentation is that of a scrotal swelling that transilluminate and usually does not cause pain (Figs. 29.27 and 29.28).
- Varicocele:
  - Occasionally, a varicocele causes mild to moderate scrotal discomfort.
  - No changes in the scrotal skin occur, but the affected hemi-scrotum may have a full appearance.
  - On physical examination, a varicocele is palpable as a “bag of worms” above a normal testis and epididymis (Fig. 29.29).

29.8 Splenogonadal Fusion

- Splenogonadal fusion is a rare congenital malformation that results from an abnormal fusion between the primitive spleen and gonad.
- Splenogonadal fusion is a rare, benign, congenital anomaly thought to occur between the fifth and eighth weeks of intrauterine life where immature splenic tissue adheres to the developing gonad, epididymis or vas deferens.
- The splenic tissue is subsequently pulled in a caudal direction with descent of the gonad.
- Karaman and Gonzales in 1996 reviewed 137 cases of splenogonadal fusion and surprisingly 37% of the patients had orchiectomy because of suspicion of a testicular tumor.
- This is of great importance and to obviate this physicians caring for these patients should be aware of this and intra-operatively if there is doubt concerning the nature of the



Figs. 29.27 and 29.28 Clinical photographs showing hydroceles in a child. This usually present with a scrotal swelling that is not painful

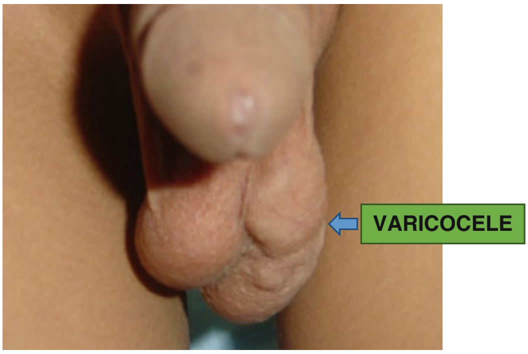


Fig. 29.29 A clinical photograph showing a left varicocele

swelling, intra-operative frozen section biopsy should be performed to avoid unnecessary orchiectomy.

- Splenogonadal fusion occurs more commonly in males with a male-to-female ratio of 15:1. This figure may of course be inaccurate due to the relative inaccessibility of the ovary to clinical examination.
- It is seen nearly always on the left side.
- Splenogonadal fusion is common in children and adolescents.
  - The number of cases reported in patients <10 years of age account for 50 % of the total cases reported.
  - The number of cases reported in patients <20 years old account for 70 %.
- Splenogonadal fusion is commonly asymptomatic discovered incidentally during routine herniotomy or orchidopexy.
- Splenogonadal fusion may presents as an asymptomatic testicular mass.
- Many of these cases however go passed unnoticed or discovered at autopsy.
- Other manifestations may include acute testicular pain and swelling caused by ectopic splenic tissue infections.
- In the pediatric age group, these patients commonly present with a scrotal swelling and may rarely present with an acute scrotal pain as a result of torsion or involvement of splenic tissue with other pathological conditions such as mumps, malaria, leukemia, trauma and infectious mononucleosis.
- Not uncommonly splenogonadal fusion is associated with other anomalies or discovered during the evaluation of these associated anomalies. This is more so with the continuous type which is known to be associated with other associated anomalies in as much as 33 % of the cases.
- There are two types of splenogonadal fusion:
  - Continuous
  - Discontinuous

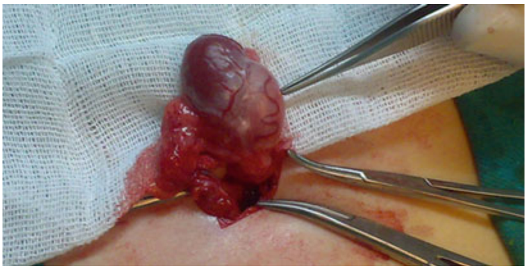
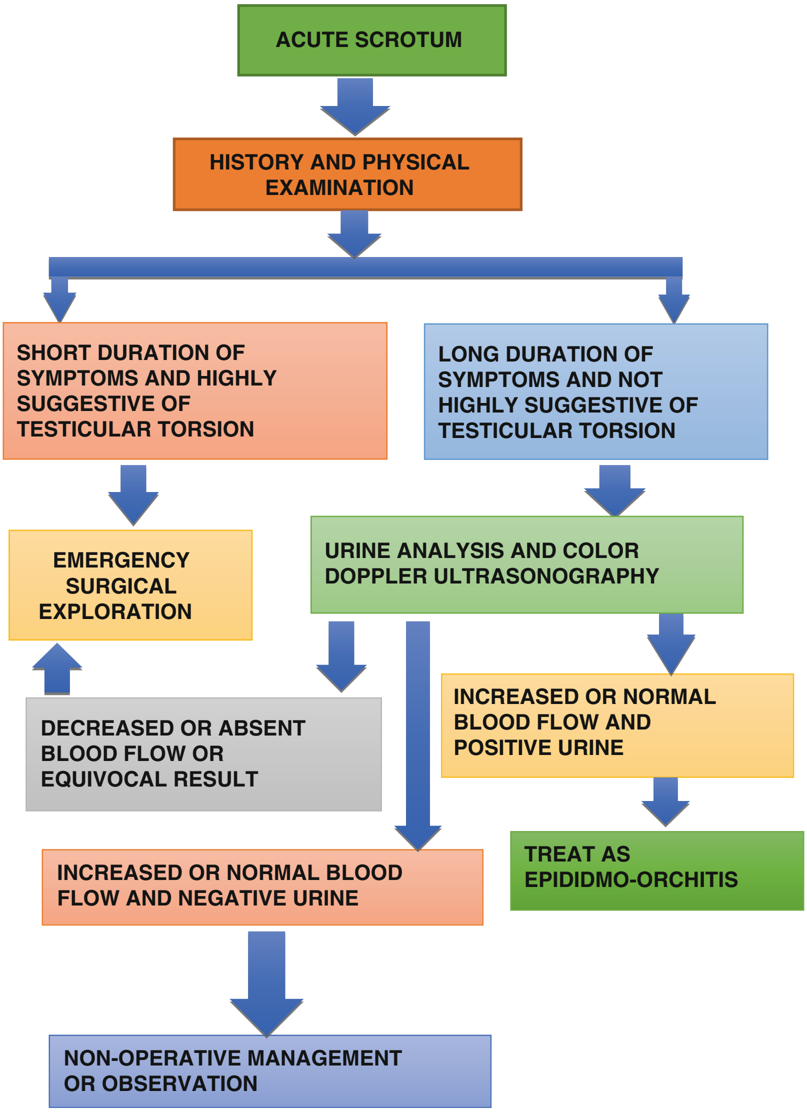


Fig. 29.30 A clinical intraoperative photograph of splenogonadal fusion diagnosed in a child with unusual testicular swelling

- In continuous splenogonadal fusion there remains a connection between the main spleen and gonad.
- In discontinuous splenogonadal fusion, ectopic splenic tissue is attached to the gonad, but there is no connection to the main spleen.
- The continuous form occurs when the normally located spleen is attached to the gonad by a discrete cord.
- In the discontinuous type the splenic tissue is attached to the gonad and completely separated from the normal spleen (Fig. 29.30).
- Both types occur with equal frequency and the discontinuous type may be discovered incidentally during herniotomy or orchidopexy or present as a scrotal swelling. Awareness of this is of great importance to avoid unnecessary orchiectomy mistaken it for a testicular tumor.
- Treatment is surgical excision and every attempt should be made to preserve the gonad at the time of dissection and excision which should not be difficult since true fusion with the gonad is rare.
- Although there have been few reports of an association of testicular neoplasms with splenogonadal fusion, it appears that this is a coincidental finding rather than an association as these tumors occurred in adults with undescended testes.
- The diagnosis of splenogonadal fusion should always be kept in mind and included in the differential diagnosis of testicular swelling in infants and children.


ACUTE SCROTUM
HISTORY AND PHYSICAL EXAMINATION
SHORT DURATION OF SYMPTOMS AND HIGHLY SUGGESTIVE OF TESTICULAR TORSION
LONG DURATION OF SYMPTOMS AND NOT HIGHLY SUGGESTIVE OF TESTICULAR TORSION
EMERGENCY SURGICAL EXPLORATION
URINE ANALYSIS AND COLOR DOPPLER ULTRASONOGRAPHY
DECREASED OR ABSENT BLOOD FLOW OR EQUIVOCAL RESULT
INCREASED OR NORMAL BLOOD FLOW AND POSITIVE URINE
TREAT AS EPIDIDMO-ORCHITIS
INCREASED OR NORMAL BLOOD FLOW AND NEGATIVE URINE
NON-OPERATIVE MANAGEMENT OR OBSERVATION

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Hydrocolpos, Vaginal Agenesis and Atresia

30

30.1 Introduction

- Hydrocolpos is the distension of the vagina caused by accumulation of fluid due to congenital vaginal obstruction.
- The obstruction is often caused by an imperforate hymen or less commonly a transverse vaginal septum.
- The fluid consists of cervical and endometrial mucus.
- In rare instances the hydrocolpos is secondary to urine accumulated through a vesicovaginal fistula proximal to the obstruction or due to the presence of urogenital sinus with collection of urine.
- The term hydrometrocolpos is when hydrocolpos is associated with fluid accumulation in the uterus.
- Vaginal atresia is a congenital abnormality of the female genital system.
- It represent a spectrum of malformations ranging from total vaginal agenesis to vaginal atresia.

30.2 Imperforate Hymen

- Imperforate hymen is the most common and most distal form of vaginal outflow obstruction.
- An imperforate hymen is a congenital malformation characterized by a hymen without an opening which completely obstructs the vagina (Fig. 30.1).
- It is caused by a failure of the hymen to perforate during fetal development.
- It is most often diagnosed in adolescent girls when menstrual blood accumulates in the vagina (hematocolpos) and sometimes also in the uterus.
- In adolescent females:
  - The most common symptoms of an imperforate hymen are cyclic pelvic pain and amenorrhea.
  - The cyclic pain is secondary to hematocolpos.
  - Other symptoms include urinary retention, constipation, back pain, nausea, and diarrhea.

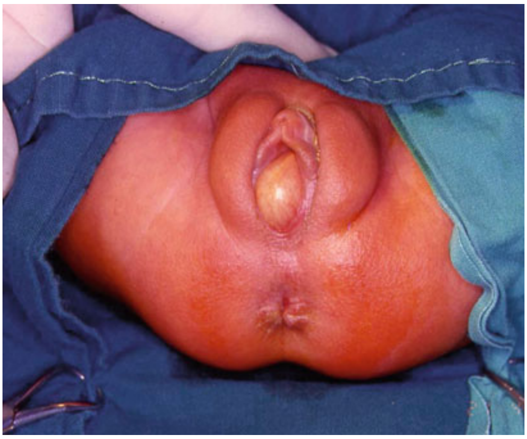

Fig. 30.1 A clinical photograph showing a newborn with imperforate hymen. Note the bulging hymenal membrane

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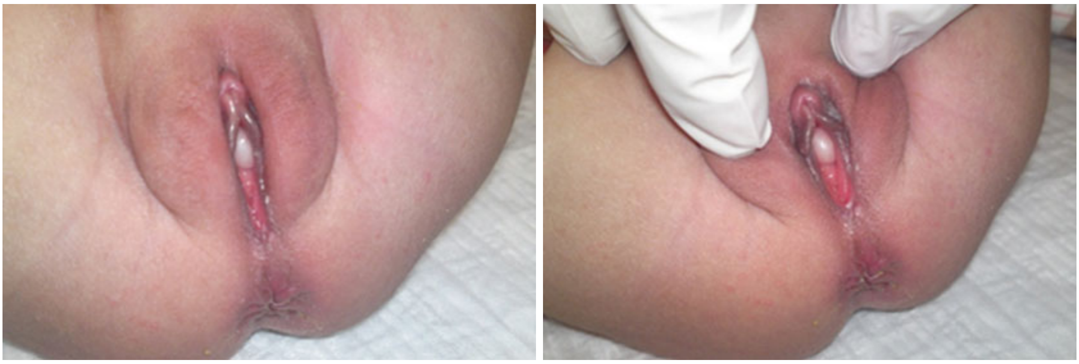
A.H. Al-Salem, *An Illustrated Guide to Pediatric Urology*, DOI 10.1007/978-3-319-44182-5_30



Figs. 30.2 and 30.3 Clinical photographs showing a newborn with imperforate hymen. Note the whitish bulging hymenal membrane

- The hymen originates from the embryonic vagina buds from the urogenital sinus.
- As a consequence, the hymen is a composite of vaginal epithelium and epithelium of the urogenital sinus interposed by mesoderm.
- Once the hymen becomes perforated or forms a central canal, it establishes a communication between the upper vaginal tract and the vestibule of the vagina.
- Normally, there are anatomic variations of the patent hymen.
  - The most common being an annular or circumferential hymen in which the hymen completely surrounds the vaginal orifice and has a central opening.
  - Other appearances of the hymen include crescentic, fimbriated, septate, cribriform, and microperforate forms.
- It is proposed that an imperforate hymen is formed during fetal development when the sinovaginal bulbs fail to canalize with the rest of the vagina. This result is a solid membrane interposed between the proximal uterovaginal tract and the introitus.
- The exact cause of imperforate hymen is not known.
- Imperforate hymen may result from failure of apoptosis due to a genetically transmitted signal, or it may be related to an inappropriate hormonal milieu.
- Familial inheritance in successive generations has been described
- Imperforate hymen is the most frequent cause of vaginal outflow obstruction, occurring in 0.1 % of infant girls.
- This vaginal outlet obstruction results in the entrapment of vaginal and uterine secretions under the influence of maternal estrogens and this becomes evident when the distensible membrane bulges between the labia.
- In adolescence, the retained secretions consist of menstrual products, and the resulting mass effect in the vagina and uterus are referred to as hematocolpos and hematometrocolpos, respectively.
- Pyocolpos (infection of a hydrocolpos) may result from an infection that is ascending through microperforations in the hymen membrane.
- Clinical presentations of imperforate hymen in newborns include:
  - An incidental finding on routine physical examination of a newborn.
  - The neonate with imperforate hymen typically presents with a bulging membrane between the labia.
  - The membrane may be white or yellow-grey because it is distended from trapped mucoid material secreted as a result of stimulation by maternal estrogen (Figs. 30.2 and 30.3).
  - In severe cases, the distention extends proximally into the uterus (hydrometrocolpos).
  - A lower abdominal midline mass may be evident on physical examination because

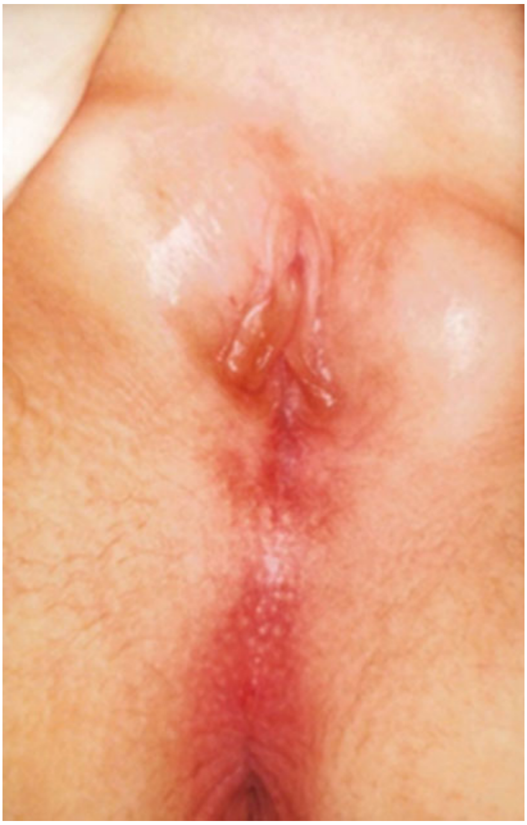


Fig. 30.4 A clinical photograph showing labial adhesions (fused labia) not to be confused with imperforate hymen

  the shallow pelvis of a neonate allows the uterus to be palpated above the pubis symphysis.
  - Hydrocolpos can lead to urinary tract infections or bladder obstruction and acute urinary retention.
- Asymptomatic imperforate hymen should not be confused with labial adhesions (fused labia) (Fig. 30.4)
- The diagnosis is made clinically and can be confirmed by ultrasonography.
- The treatment is hymenotomy in those with evidence of obstruction or urinary symptoms.
- Others advocate observation throughout childhood, with a planned hymenotomy after the onset of puberty.
- If a patient is diagnosed with an asymptomatic imperforate hymen in infancy or childhood beyond the neonatal period, the optimal time for surgical repair is after the onset of puberty and prior to menarche.

30.3 Vaginal Atresia

- This is a birth defect where the vagina is blocked off to varying degrees.
- It is often associated with syndromes such as:
  - Bardet-Biedl syndrome
  - Fraser syndrome
  - Mayer-Rokitansky-Küstner-Hauser (MRKH) syndrome
- Mayer-Rokitansky-Küstner-Hauser (MRKH) syndrome: This syndrome is characterized by the followings:
  - Absent uterus
  - A deformed or absent vagina
  - Normal ovaries
  - Normal external genitalia.
- Vaginal atresia is estimated to occur in 1 in 5,000–10,000 live female births.
- Vaginal atresia is a congenital developmental defect resulting in uterovaginal outflow obstruction which can present either:
  - In the neonatal period with hydrocolpos as a result of accumulation of secretions from the normal cervical glands under the influence of maternal hormones. Extension of fluid accumulation to involve the uterus will result in hydrometrocolpos.
  - Hydrocolpos can be complicated by infection leading to pyocolpos.
  - In adolescence with hematocolpos as a result of obstruction to the normal menstrual flow or with primary amenorrhea. Vaginal atresia is reported to be the second most common cause of primary amenorrhea.

30.4 Classification

- Vaginal atresia is classified anatomically into three types:
  - Vaginal agenesis

    - Mayer-Rokitansky-Küster-Hauser (MRKH) syndrome
  - Proximal vaginal atresia
  - Distal vaginal atresia

30.5 Associated Anomalies

- Vagina atresia and agenesis are congenital anomalies of the female genitourinary tract and may occur as:
- An isolated developmental defect
- Part of a complex of developmental anomalies such as:
  - The Rokitansky-Mayer-Küster-Hauser (RMKH) syndrome
  - The Bardet-Biedl syndrome
  - The Kaufman-McKusick syndrome
  - The Fraser syndrome
  - The Winters syndrome.
- Renal anomalies:
  - Occur in 30 % of patients with RMKH syndrome.
  - These anomalies include:
    - Unilateral agenesis of the kidney
    - Ectopic kidneys
    - Horseshoe kidney
    - Crossed-fused renal ectopia
- Skeletal anomalies:
  - Fused vertebrae
  - Anomalies of the ribs and limbs

30.6 Embryology

- Normally there are two pairs of ducts in the embryo, the wollfian and Mullerian ducts.
- These are responsible for the development of the male (Wollfian) and female (Mullerian) internal genitalia.
- In the female embryo:
  - The absence of testes which secret testesterone and Mullerian inhibiting substance (MIS) allow development and differentiation of the müllerian duct system and regression of the wolffian ducts.
  - The müllerian duct elongate and reaches the urogenital sinus by 9 weeks' gestation, and form the uterovaginal canal.
  - The two müllerian ducts proceed caudad to cephalad and fuse together to form the uterine cavity and upper two thirds of the vagina.
  - The fallopian tubes are formed from the cephalic remnants of the müllerian duct.
  - The sinovaginal bulbs form as bilateral endodermal invaginations.
  - Cephalic growth of the sinovaginal bulb and their fusion with the vaginal cord forms the vaginal plate.
  - Canalization of the uterovaginal canal is believed to occur from the caudal to the cephalic aspect, with an epithelial lining derived from the urogenital sinus.
  - Vaginal development is completed by 5 months' gestation and their musculature is derived from surrounding mesenchyme.
  - The vagina is embryologically derived from both the müllerian ducts and the urogenital sinus.
  - It is postulated that the upper two thirds of the vagina are derived from the mullerian ducts and the lower third is derived from the urogenital sinus.
- Failure of this normal development at any stage can lead to genital abnormalites:
  - Persistent Mullerian duct syndrome: This is seen in male children as a result of failure of secretion of MIS or failure of the receptors to respond to MIS. It is characterized by the presence of a uterus, upper part of vagina and fallopian tubes in a phenotypically and genetically normal male.
  - A septate uterus: This results from failure of the septum between the two mullerian ducts to regress.
  - Arcuate, bicornuate, or didelphic uteri: These result from incomplete fusion of the müllerian ducts.
  - Uterovaginal atresia: This results from failure of the caudal development of the müllerian ducts.
  - A transverse vaginal septum: This results from failures at the level of the vaginal plate.
  - Vaginal atresia: This occurs when the caudal portion of the vagina, contributed by the urogenital sinus, fails to form. This cau-

dal portion of the vagina is replaced with fibrous tissue.
  - Lower vaginal atresia is a type of vagina atresia where the lower 3rd of the vagina fails to develop.
  - It is usually not considered a type of Mullerian duct anomaly. It occurs from a failure of recanalisation of the urogenital sinus.
  - Patients with RMKH syndrome and vaginal atresia are phenotypically and genotypically female with a 46, XX karyotype. However, a familial association suggests autosomal dominant transmission of a mutant gene by male relatives.
  - Mayer-Rokitansky-Küster-Hauser (MRKH) syndrome is defined as Müllerian aplasia with vaginal agenesis and uterine remnants.
  - It is commonly associated with renal and sometimes vertebral anomalies. The MRKH syndrome or distal vaginal atresia is sometimes associated with anorectal malformations.

30.7 Clinical Features

- The clinical presentation of vaginal atresia is variable.
- The majority of neonates with vaginal atresia are asymptomatic but they my present with:
  - An abdominal mass (Figs. 30.5 and 30.6):
    - This is secondary to hydrocolpos or hydrometrocolpos.
    - It may be discovered during routine antenatal ultrasound
    - This may be discovered clinically immediately after delivery or during the first few weeks of life.
  - Sepsis
  - Respiratory distress.
- Vaginal atresia may remain asymptomatic till adolescence and the presentation may include:
  - Amenorrhea
  - Cyclical abdominal pain
  - Difficulty in voiding
  - An abdominopelvic mass
  - Backache
- The presence of polydactly and congenital heart disease is suggestive of an associated syndrome (McKusick-Kaufman syndrome, Bardet-Biedl syndrome). The polydactly can affect either lower and upper limbs or only one limb (Figs. 30.7, 30.8, 30.9, and 30.10).
- Perineal examination may reveal:
  - Normal external genitalia
  - No apparent vaginal orifice and no hymen
  - Development of secondary sex characteristics in the adolescent.
  - An isolated vaginal dimple or a small vaginal pouch with a normal hymenal ring may be seen.
  - Abnormal anal opening (Figs. 30.11 and 30.12)
  - Labial fusion may obscure the anatomy of some patients and be confused with vaginal atresia.
  - The presence of posterior labial fusion and enlarged clitoris is suggestive of congenital adrenal hyperplasia.

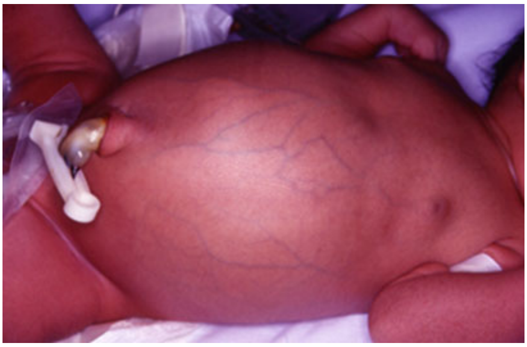


Fig. 30.5 A clinical photograph showing a newborn with abdominal mass secondary to hydrometrocolpos

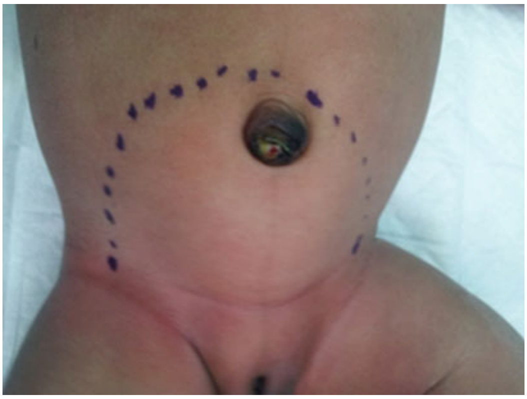
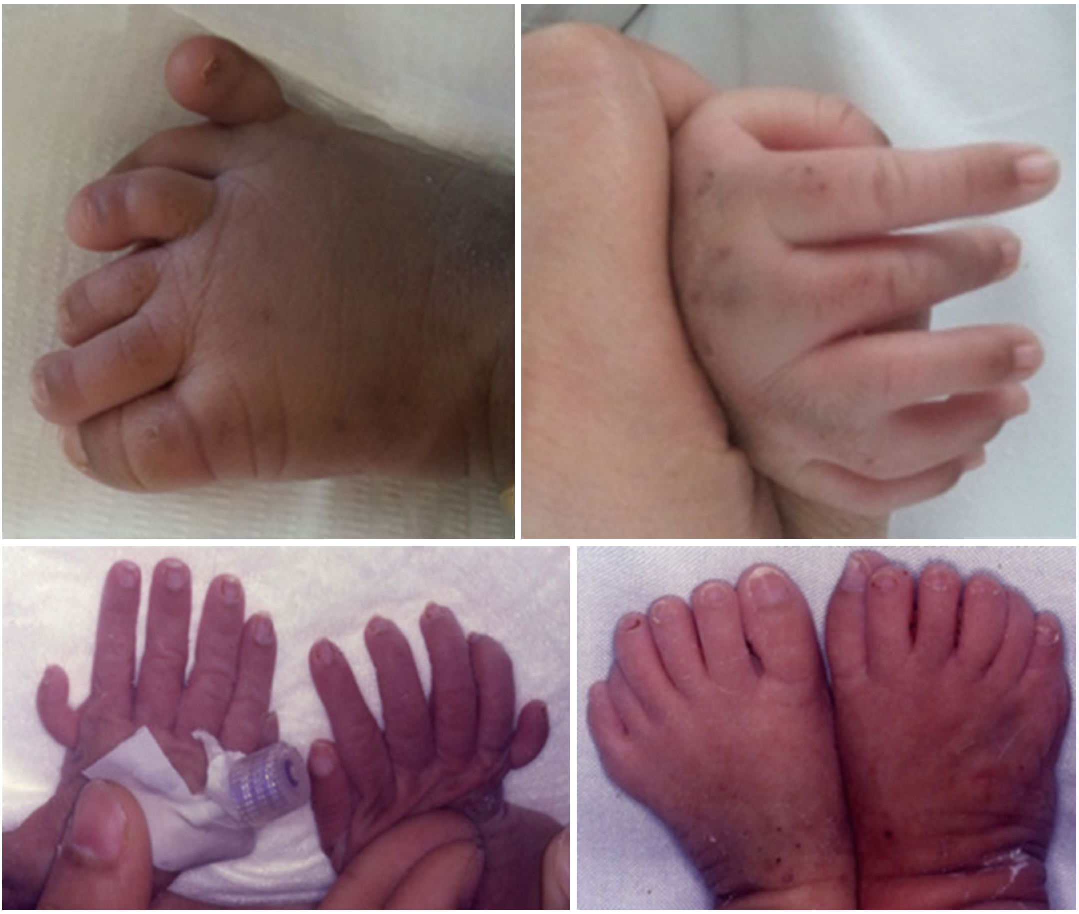
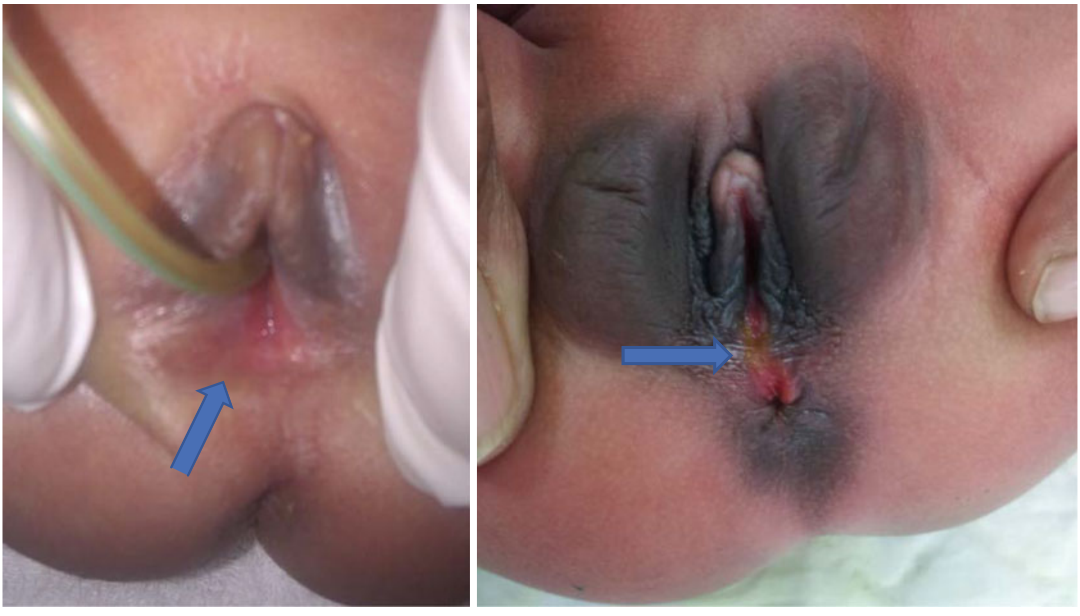


Fig. 30.6 A clinical photograph showing a newborn with abdominal mass secondary to hydrometrocolpos. The mass is arising from the pelvis upwards



Figs. 30.7, 30.8, 30.9, and 30.10 Clinical photographs showing polydactly both upper and lower limbs

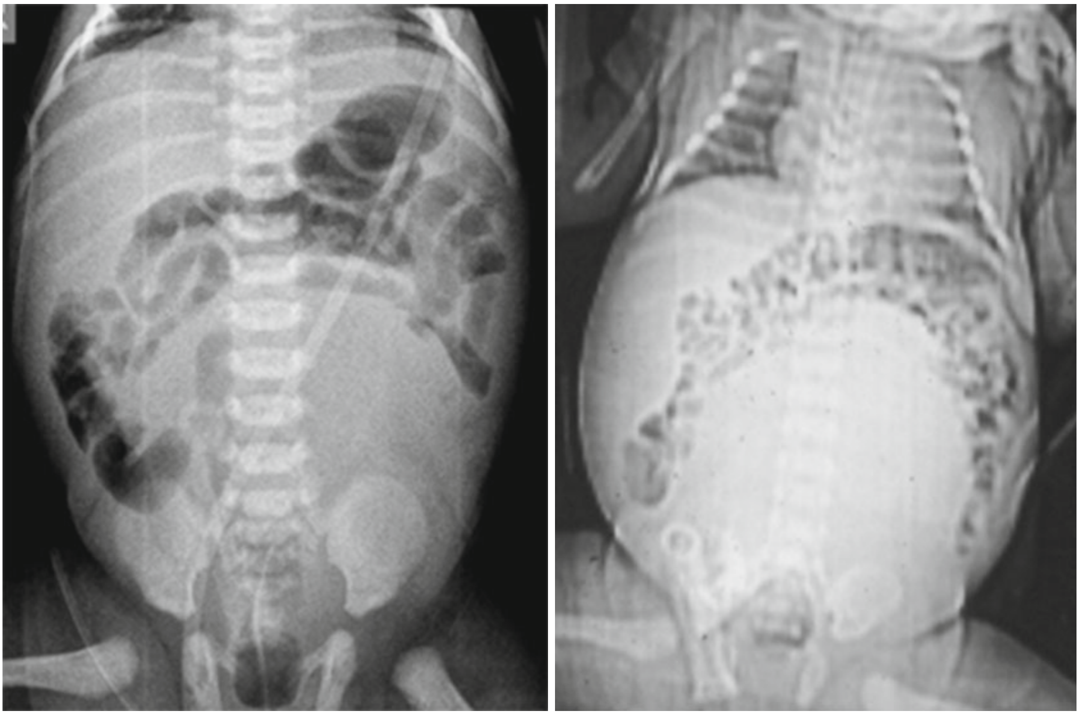


Figs. 30.11 and 30.12 Clinical photographs showing a newborn with vaginal atresia. Note the absence of a vaginal opening. Note also the anteriorly placed anus in the first picture

- McKusick-Kaufman syndrome:
  - This is an autosomal recessive disorder.
  - It is characterized by:
    - Hydrometrocolpos secondary to vaginal atresia.
    - Postaxial polydactyly
    - Imperforated anus
    - Congenital heart defects.
- Bardet-Biedl syndrome:
  - This is an autosomal recessive disorders.
  - It is characterized by:
    - Vaginal atresia
    - Retinal dystrophy or retinitis pigmentosa
    - Postaxial polydactyly
    - Obesity
    - Nephropathy
    - Mental disturbances
- Fraser syndrome:
  - Fraser syndrome (also known as Meyer-Schwickerath's syndrome, Fraser-François syndrome, or Ullrich-Feichtiger syndrome) is an autosomal recessive congenital disorder.
  - It is characterized by:
    - Cryptophthalmos (where the eyelids fail to separate in each eye)
    - Vaginal atresia
    - Other malformations of the genitalia including micropenis, and cryptorchidism in males and clitoromegaly in females.
    - Congenital malformations of the nose, ears, larynx and renal system.
    - Mental retardation
    - Syndactly
- Winters syndrome:
  - It is characterized by ear anomalies and vaginal atresia.

30.8 Investigations

- In newborns, it is important to define preoperatively the anatomic abnormality leading to the hydrometrocolpos.
- Whereas imperforate hymen is clinically evident and simple to treat, vaginal atresia is more complex to define and manage.
- Abdominal radiograph (Figs. 30.13 and 30.14):
  - This may reveal a soft tissue density pushing the bowel to the side and upwards.



Figs. 30.13 and 30.14 Abdominal x-rays showing a soft tissue mass representing the dilated vagina and pushing the bowel upwards

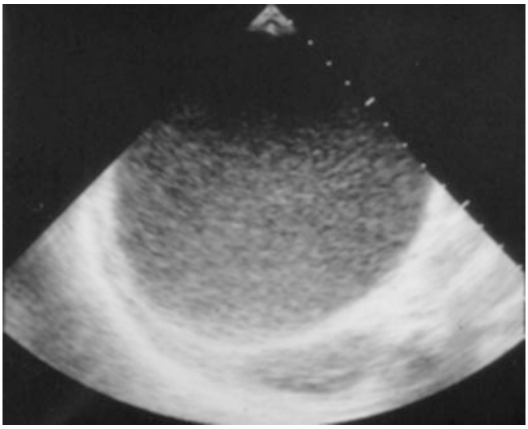


Fig. 30.15 Abdominal ultrasound showing a dilated vagina (hydrocolpos) secondary to vaginal atresia

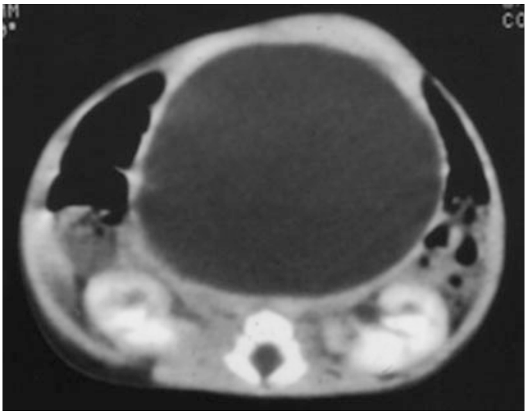
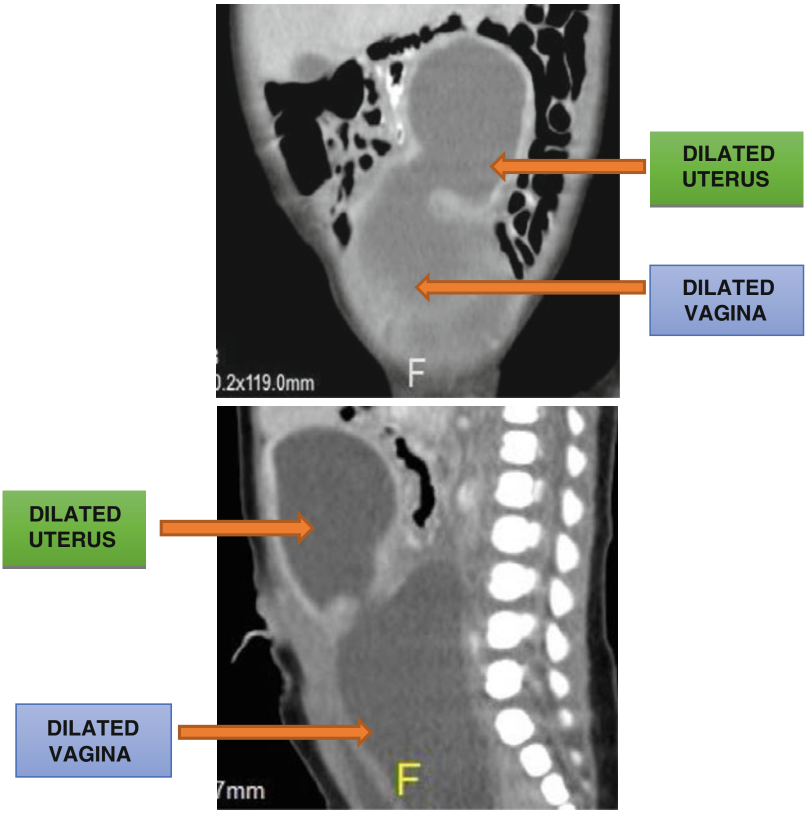
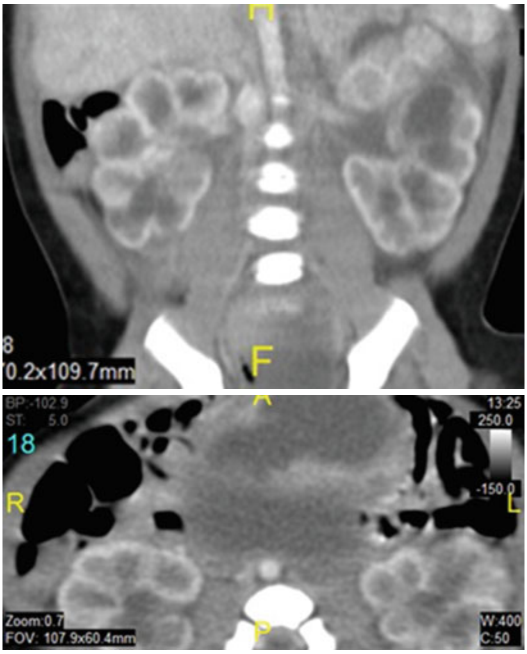


Fig. 30.16 Abdominal CT-scan showing a very large hydrocolpos



Figs. 30.17 and 30.18 Abdominal CT-scan showing hydrometrocolpos secondary to vaginal atresia

- Abdominal and pelvic ultrasonography (Fig. 30.15):
  - This is a simple, non-invasive investigation for patients with suspected vaginal atresia.
  - It is valuable to define the ovaries, uterus, and proximal vagina.
  - The presence of hydrocolpos or hydrometrocolpos can be detected easily with ultrasound.
  - It is also useful to evaluate the kidneys, ureter and urinary bladder and associated anomalies.
- Abdominal and pelvic CT-scan (Figs. 30.16, 30.17, 30.18, 30.19, and 30.20):



Figs. 30.19 and 30.20 Abdominal CT-scan showing hydronephrosis secondary to pressure from the dilated vagina

  - This gives more detailed information regarding the anatomy and etiology.
- Intravenous urography is rarely used (Fig. 30.21).
- MRI (Figs. 30.22, 30.23, and 30.24):
  - This has been reported to be more valuable than ultrasound and CT-scan in delineating the vaginal anatomical defect and the associated hydroureter and hydronephrosis.
- Genitography is an unnecessary invasive investigation that may be harmful leading to secondary infection with subsequent pyometrocolpos (Figs. 30.25 and 30.26).
- This must be kept in mind when evaluating hydrometrocolpos as there is a possibility of secondary infection and development of pyometrocolpos which is a serious complication.
- Laparoscopy may be necessary to evaluate the uterus and adnexal structures if they are not clearly identified on ultrasound, CT-scan or MRI.

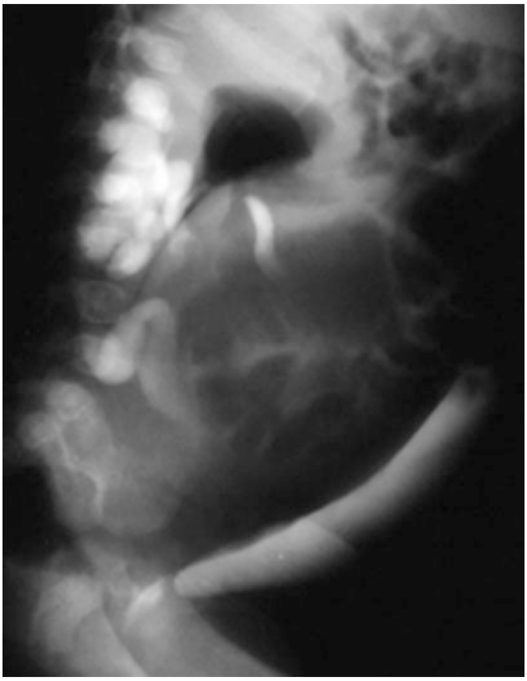


Fig. 30.21 Intravenous urography showing dilated ureters and hydronephrosis secondary to pressure from hydrometrocolpos

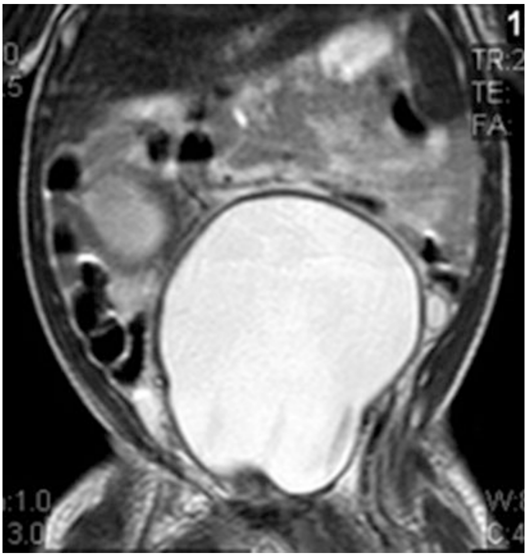
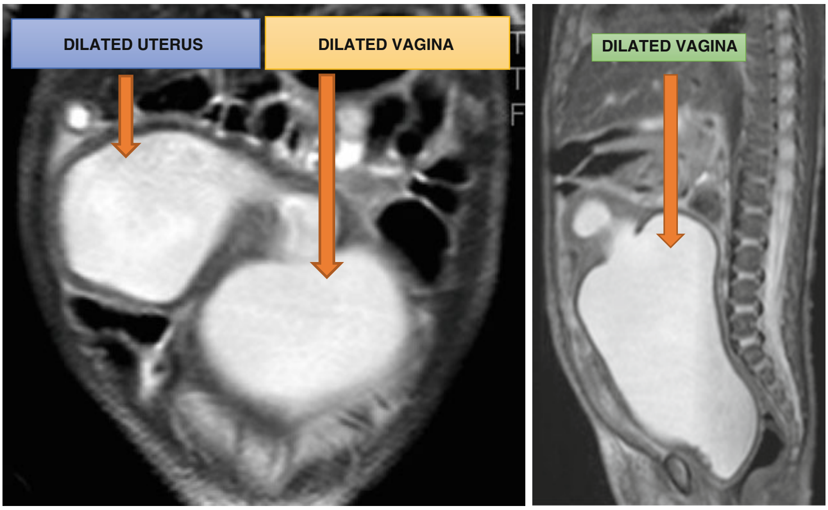
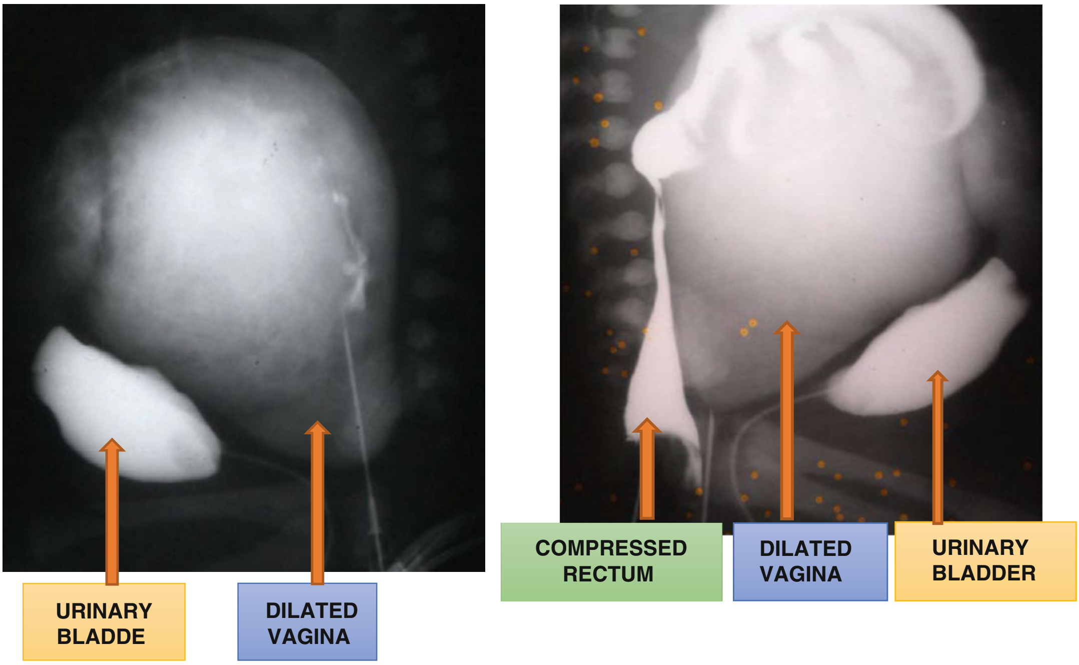


Fig. 30.22 Abdominal MRI showing a very large hydrocolpos


DILATED UTERUS
DILATED VAGINA
DILATED VAGINA

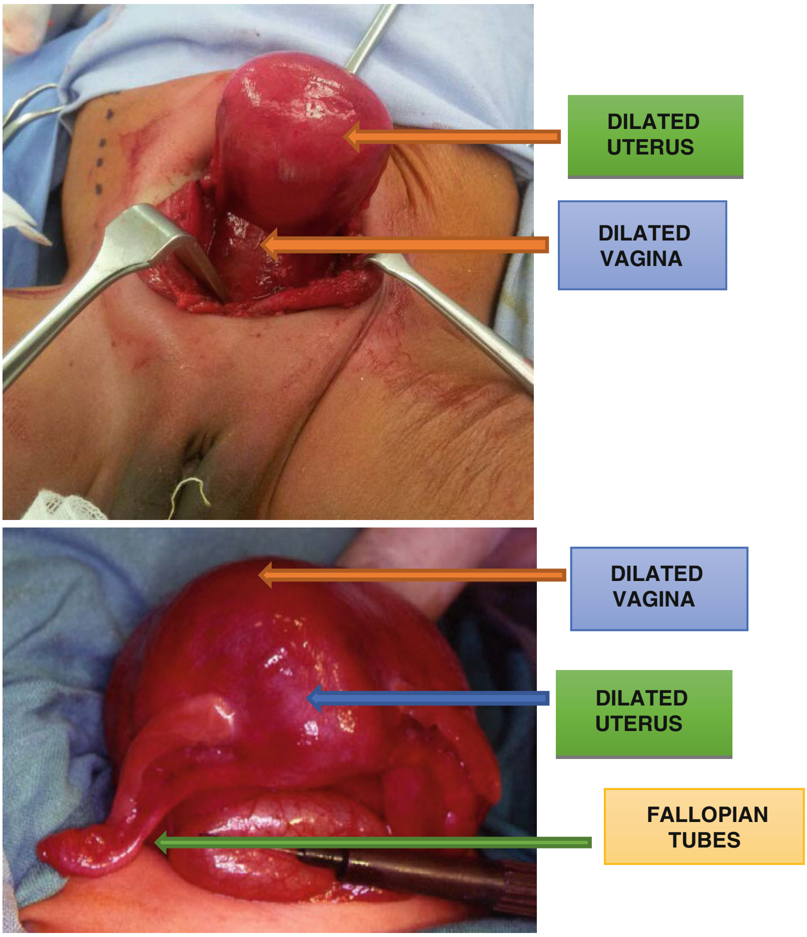
Figs. 30.23 and 30.24 Abdominal MRI showing hydrometrocolpos secondary to vaginal atresia


URINARY BLADDE
DILATED VAGINA
COMPRESSED RECTUM
DILATED VAGINA
URINARY BLADDER

Figs. 30.25 and 30.26 Contrast study showing massive hydrocolpos compressing the colon posteriorly and the urinary bladder anteriorly. The accumulated fluid can extend into the uterus causing hydrometrocolpos and sometimes spills into the peritoneal cavity via the Fallopian tubes

30.9 Management

- The goals of surgical management in patients with vaginal atresia are:
  - To relieve vaginal obstruction
  - To restore normal anatomy and a normal sex life
  - To preserve the patient's reproductive potential
- The timing of surgery depends on the patient's presentation.
- In newborns with hydrocolpos, emergency drainage of the hydrocolpos should be done or more preferably, an abdominoperineal vaginal pull-through can be done as a single stage (Figs. 30.25, 30.26, 30.27, 30.28, 30.29,



Figs. 30.27 and 30.28 Clinical intra-operative photographs showing hydrometrocolpos secondary to vaginal atresia

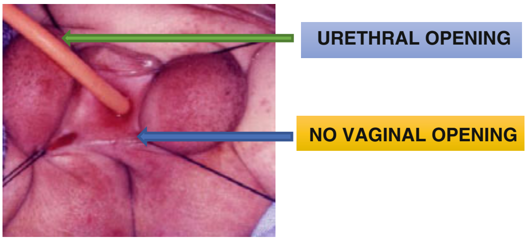
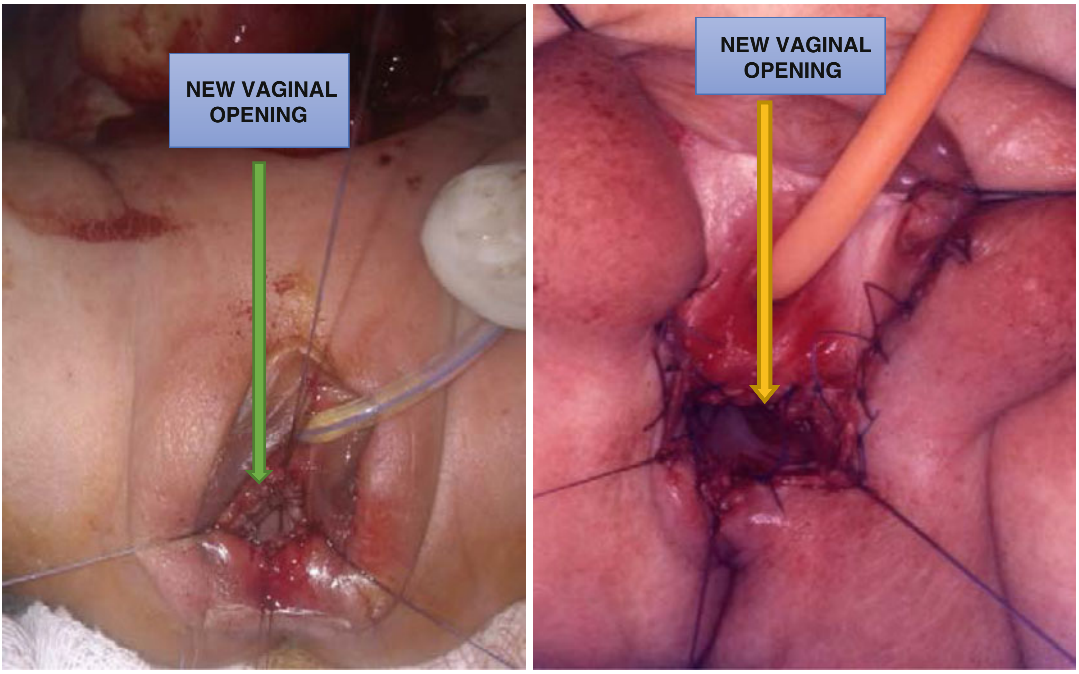


Fig. 30.29 A clinical photograph showing a newborn girl with vaginal atresia. Note the Foley's catheter in the urethra. Note also the absence of vaginal opening

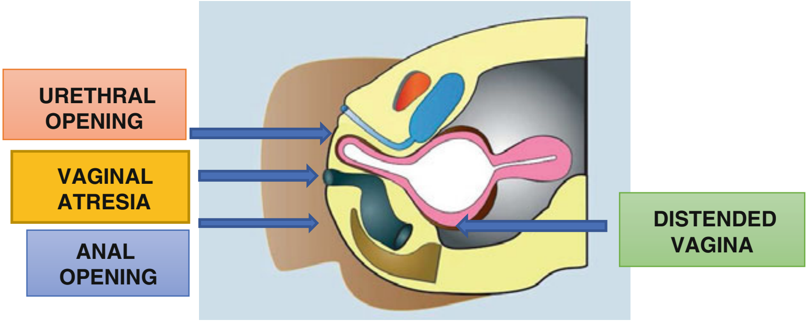
30.30, 30.31, 30.32, 30.33, 30.34, 30.35, 30.36, 30.37, 30.38, and 30.39):

- A Foley's catheter is inserted.
- Laparotomy is done through a lower transverse abdominal incision.
- The hydrmetrocolpos is defined and the anatomy is outlined.
- The distended vagina is opened anteriorly and emptied.
- A new vaginal opening is created in the perineum using a semicircular or transverse incision at the hymenal ring.
- Using blunt and sharp dissection from below toward the peritoneal cavity, a channel is created.
- At this stage, it is important to protect the rectum.
- A Hegar dilator is passed into the distended vagina and the posterior wall is pushed downwards till the newly created vaginal opening,
- The vaginal wall is grasped with a babcock, opened and a single-layer anastomosis is created between the edges and the hymenal regions by using absorbable sutures.


NEW VAGINAL OPENING
NEW VAGINAL OPENING

Figs. 30.30 and 30.31 Clinical intra-operative photographs showing vagina atresia and abdominoperineal vaginal pull through. Note the new vaginal opening

Fig. 30.32 Diagrammatic representation of vaginal atresia


URETHRAL OPENING
VAGINAL ATRESIA
ANAL OPENING
DISTENDED VAGINA

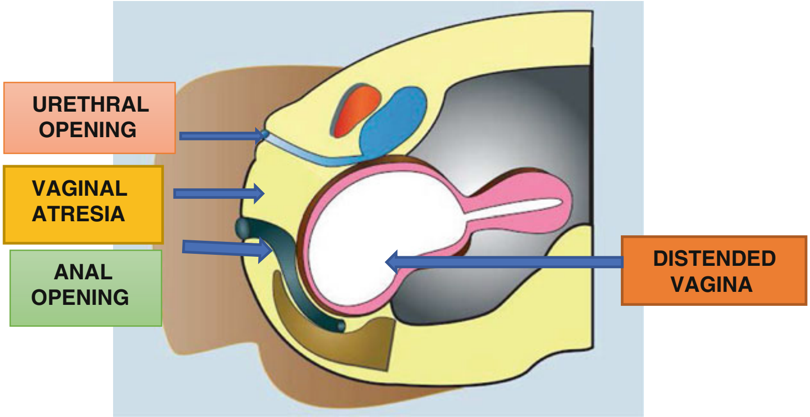
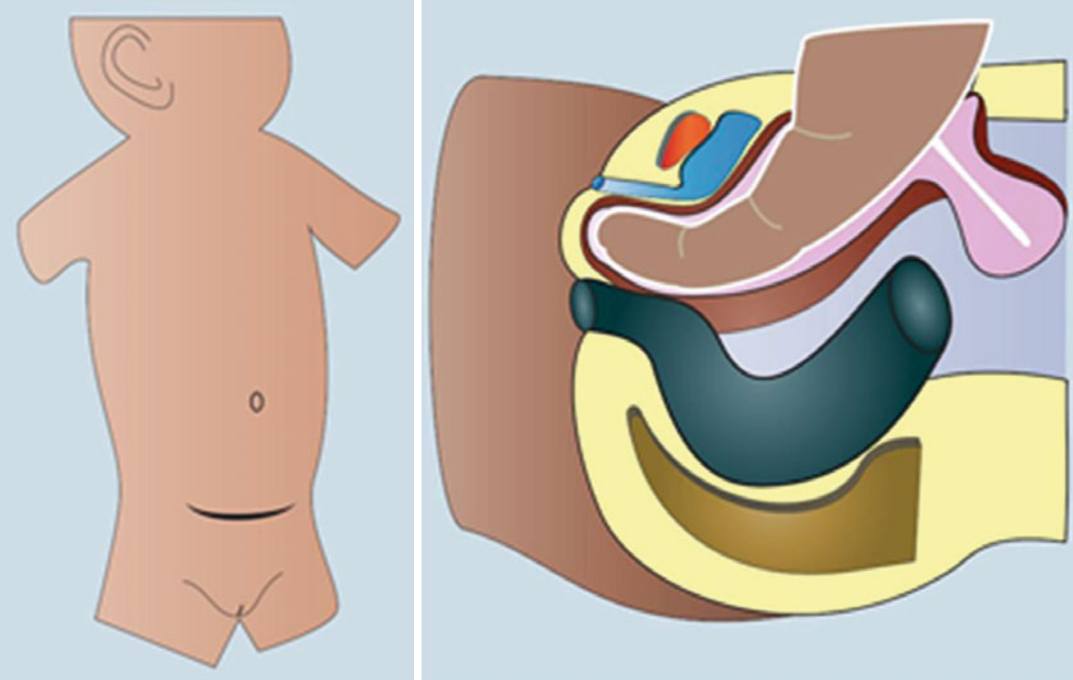
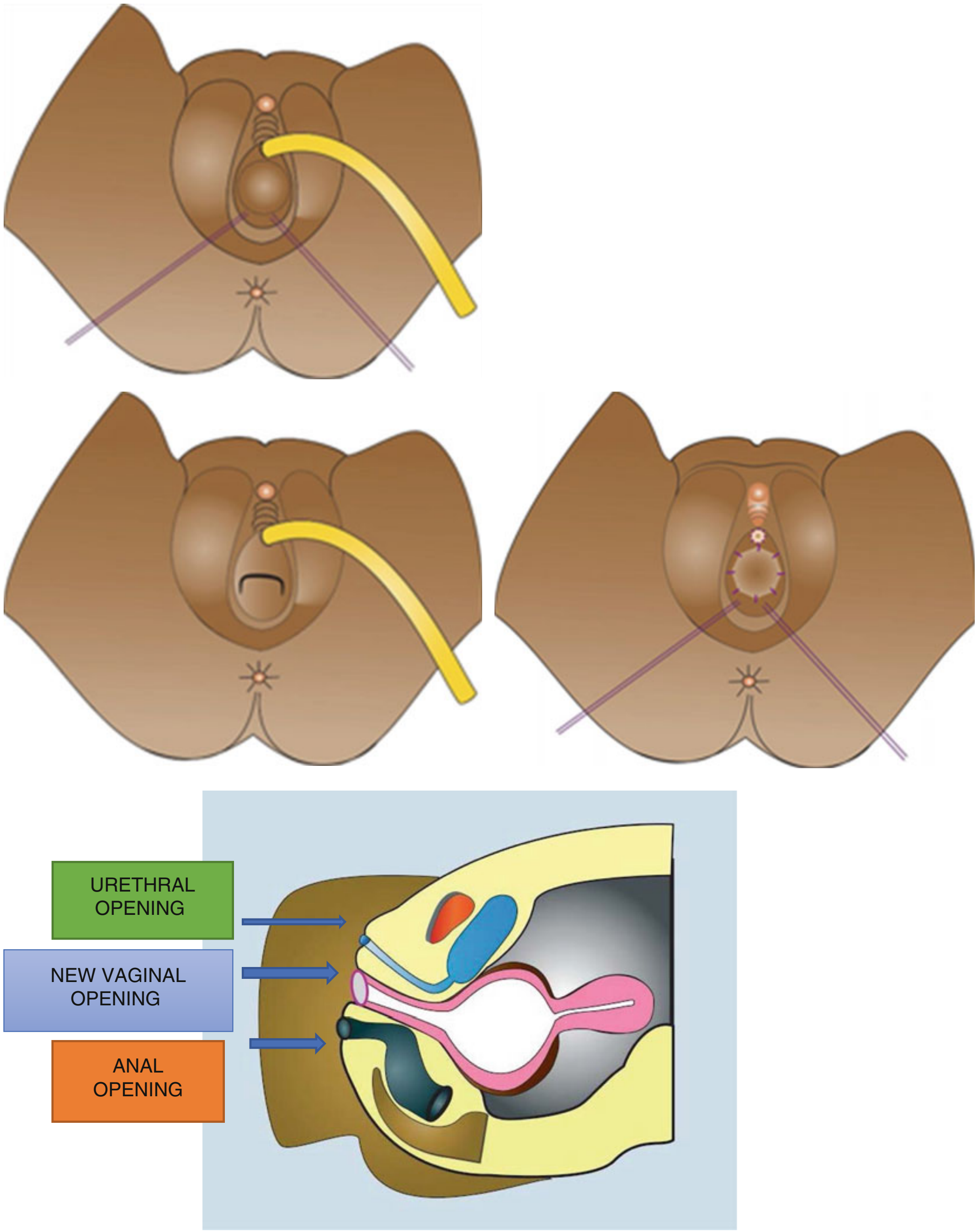

URETHRAL OPENING
VAGINAL ATRESIA
ANAL OPENING
DISTENDED VAGINA

Fig. 30.33 Diagrammatic representation of vaginal atresia. Note the markedly distended vagina and the distance to the perineum



Figs. 30.34 and 30.35 Diagrammatic photograph showing the site of incision and the finger in the dilated already opened vagina. A hegar dilator can be used as a guide

- In those without hydrocolpos, vaginal reconstruction is delayed till late childhood or early adolesence.
- In those with vaginal agenesis, there are several reconstruction procedures to create a new vagina by using either extra-abdominal tissues or intra-abdominal tissues.
- There is however, no consensus regarding the ideal method for creating a functional vagina:
  - The Abbe-McIndoe operation. With this procedure, a split-thickness skin graft is taken from the buttock and used to create the neovagina.
  - Musculocutaneous flaps using the rectus and gracilis muscles are now rarely used to create the neovagina.
  - Vulvovaginoplasty using tissue expanders.
  - Intestinal segments, typically derived from the sigmoid colon and rarely the ileum, cecum, and rectosigmoid colon.
    - A segment of the sigmoid colon is chosen, with a major vascular pedicle supplying the mesenteric arcade.
    - This segment is divided, and the colon continuity is restored by primary end to end anastomosis.
    - The proximal end of the segment is closed in two layers.
    - A new vaginal opening is created in the perineum using a circular or cruciate incision at the hymenal ring.
    - Using blunt and sharp dissection from below toward the peritoneal cavity, a channel is created through which the sigmoid segment is passed.
    - The sigmoid colon segment can be passed in an isoperistaltic or reverse peristaleisis depending on the vascular supply and length of the mesenteric pedicle.
    - A single-layer anastomosis is created to the hymenal regions by using absorbable sutures.
    - Attempts are made to extraperitonealize the sigmoid colon segment.
    - A Vaseline pack is placed in the neovagina to maintain apposition to the dissected tissues.


URETHRAL OPENING
NEW VAGINAL OPENING
ANAL OPENING

Figs. 30.36, 30.37, 30.38, and 30.39 Diagrammatic photographs showing the perineal stage of the vaginoplasty and the incision used to create the opening to the peritoneal cavity. The vaginal wall is pulled through this opening, opened and sutured to the margins. Note the finally constructed vaginal opening

  - This procedure is known to be associated with complications, mainly excess mucous drainage and the potential for prolapse.
- Laparoscopic Vecchietti procedure. This procedure uses an acrylic olive that is placed against the vaginal dimple, traction is applied to the olive using an attraction device.

Further Reading

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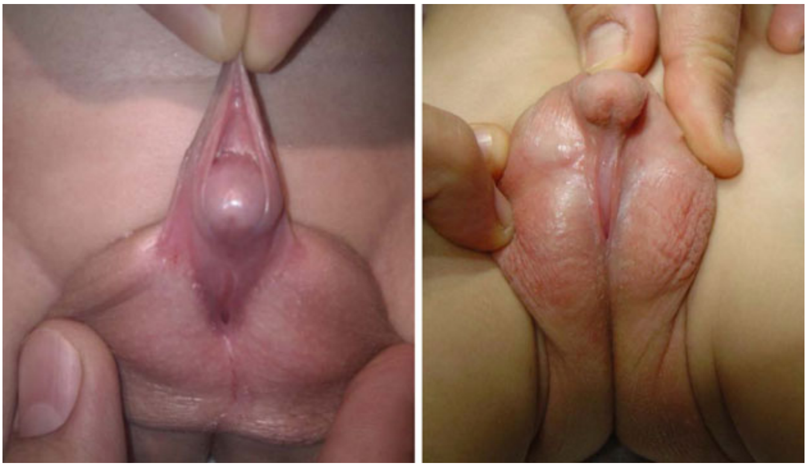
Disorders of Sexual Development

31

31.1 Introduction

- The birth of a new baby is one of the most dramatic events in a family, and the first question is usually "is it a boy or a girl?"
- When a child is born with ambiguous external genitalia it often comes as a surprise for the parents and diagnostic dilemma for the treating physicians.
- It is also considered as an endocrine emergency situation presenting a problem of sex assignment.
- It is important for clinicians to promptly make an accurate diagnosis and counsel parents on therapeutic options.
- It is also important to understand the psychological and social implications of gender assignment in some of these patients.
- In the past several names such as intersex or ambiguous genitalia were used to describe disorders of sexual development but they were not accurately descriptive.
- Intersex (Figs. 31.1, 31.2, 31.3, 31.4, 31.5, 31.6, and 31.7):
  - Intersex literally means that the body is between the two sexes, male and female.
  - This is a term that is no longer used; it has now been replaced by disorders of sexual development (DSD).



Figs. 31.1 and 31.2 Clinical photographs showing severe hypospadias with abnormal genitalia

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A.H. Al-Salem, *An Illustrated Guide to Pediatric Urology*, DOI 10.1007/978-3-319-44182-5_31

- In the past the term "hermaphrodite" was sometimes erroneously used to describe people with intersex/DSD conditions. The term hermaphroditism, was used after the Greek god of sexuality Hermes and the goddess of love and sexuality, Aphrodite. The correct technical definition of a hermaphrodite is a single organism that has complete sets of both male and female sexual organs. This term is also no longer used to describe humans.
- The nomenclatures such as 'intersex', 'hermaphrodite', and 'pseudohermaphrodite' are no longer used. They are confusing terms and could be perceived to be pejorative by some affected families.

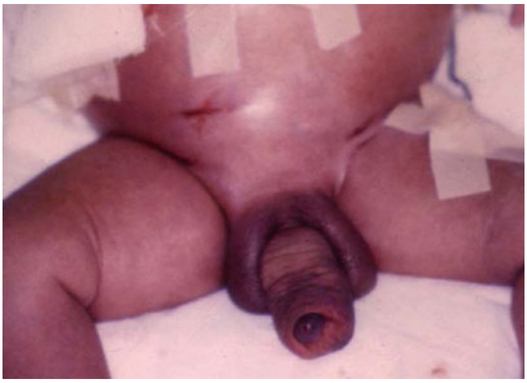
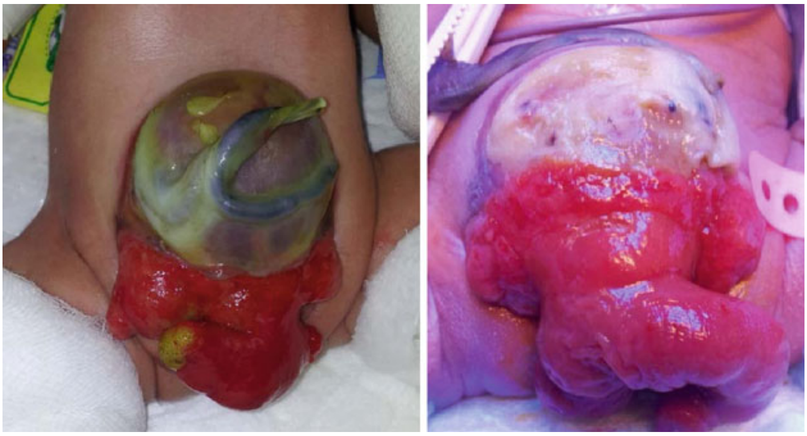


Fig. 31.3 A clinical photograph of a patient with DSD. It is difficult to decide whether this is a true male or not. This patient was investigated and found to have severe virilization secondary to congenital adrenal hyperplasia leading to enlargement of the clitoris resembling a male penis

- All these were replaced by the term Disorders of Sexual Development (DSD).
- This was coined by International Consensus Conference on Intersex organized by the Lawson Wilkins Pediatric Endocrine Society and the European Society for Pediatric Endocrinology in 2006.
- It replaces the earlier terms Intersex and ambiguous genitalia which were controversial and associated with a lot of social stigma and confusion.
- Disorders of sex development (DSD) are defined as congenital conditions in which development of chromosomal, gonadal, or anatomical sex is atypical.
- The use of the term disorder of sex development (DSD) is controversial among many activists and community organizations.
- Although there are potential criticisms to the new nomenclature, the DSD terminology has been generally accepted and is now popularly used in the literature.
- The medical term disorders of sex development (DSDs) is used to describe individuals with an atypical composition of chromosomal, gonadal and phenotypic sex, which leads to differences in the development of the urogenital tract and reproductive system.
- The term DSD has a comprehensive definition including any problem noted at birth in which



Figs. 31.4 and 31.5 Clinical photographs of two new born with cloacal exstrophy. Note there are no clear external genitalia and these patients need further evaluation prior to sex assignment. The external genitalia in these patients are usually small and not well developed

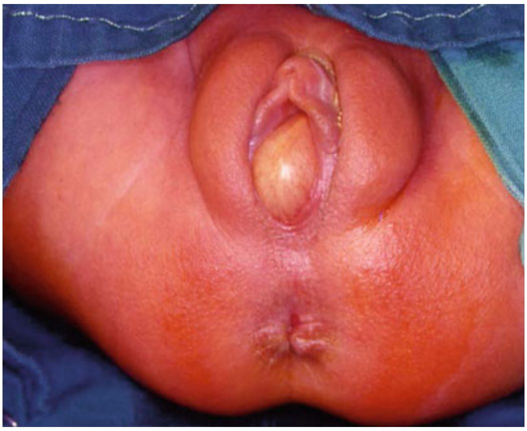


Fig. 31.6 Clinical photograph of a newborn with imperforated hymen with hydrocolpos causing abnormalities of external genitalia

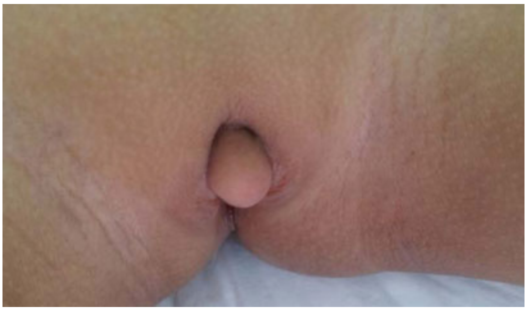
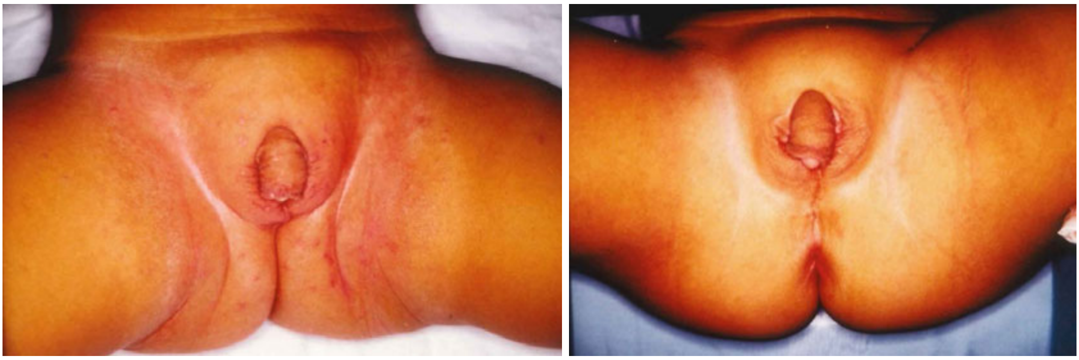


Fig. 31.7 A clinical photograph showing abnormal external genitalis. This female patient was found to have a dermoid cyst over the clitoris causing abnormaliities of the external genitalia

the genitalia are atypical in relation to the chromosomes or gonads. The karyotype is used as a prefix defining the classification of DSD.

- The newly proposed terminology and classifications have eliminated some confusion for both the patient and the family, as well as for health professionals.
- DSDs are rare and complex.
- It is estimated that the overall incidence of DSDs is 1 in 4,500–5,500 live births.
- Congenital adrenal hyperplasia (CAH) and mixed gonadal dysgenesis are the most common causes of ambiguous genitalia, constituting approximately over 50 % of all cases of genital ambiguity in the newborn period (Figs. 31.8 and 31.9).
- The incidence of CAH and mixed gonadal dysgenesis is 1:15,000 and 1:10,000, respectively.
- Currently, many countries screen newborns for CAH by use of filter-paper blood spot 17-hydroxyprogesterone measurements.
- Disorders of sexual development includes a variety of conditions in which the reproductive system or the external genitalia are not normal for a female or male.
- There are three general descriptive terms to describe the sex of a person:
  - Genotypic sex (Chromosomal sex): This refers to the sex based on the number of sex chromosomes. This depends on the presence of 46,XX or 46,XY chormosomes.



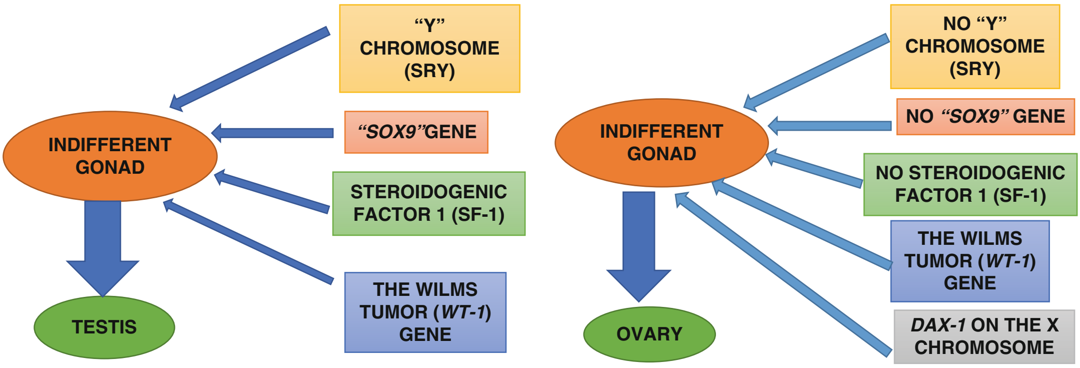
Figs. 31.8 and 31.9 Clinical photographs showing two patients with congenital adrenal hyperplasia. Note the abnormal external genitalia which show severe virilization

  - Anatomical sex (Gonadal sex): This refers to the sex according to the gonadal differentiation. This depends on the presence of a uterus, ovaries and tubes or testes, epididymis, seminal vesicles, ejaculatory ducts and prostate.
  - Phenotypic sex: This refers to the sex based on the external anatomy of the genitalia. This results from the differentiation of the external genitalia under the influence of sex-determining genes and hormones.
- Abnormalities in any of these result in a range of conditions that lead to abnormal development of the sex organs and genitalia (Disorders of sex development).
- Children with DSD often have both male and female characteristics internally as well as externally.
- Gender identity:
  - This refers to the individual's perception about his/her own gender. In some individuals, gender identity is different from the phenotypic sex.
- When a child is born with DSD, the gender may not be obvious.
- The development of sex organs and external genitalia is a very complex process that starts at around 7–8 weeks of pregnancy in the developing fetus and is complete by 12 weeks.
- Great advances have been made over recent years in understanding the genetics and pathology of DSD.
- The Chicago Consensus new nomenclature is based on the primary genetic defect.
- It includes three broad categories:
  1. Sex chromosome DSD
  2. 46, XX DSD
  3. 46, XY DSD
- The most common DSD is Congenital Adrenal Hyperplasia (CAH).
  - This results in a female (XX chromosomes) having genitals that look somewhat masculine.
  - In mild cases, CAH results in a slightly enlarged clitoris.
  - In more severe cases it can be difficult to decide whether a baby is male or female.
  - Most children with CAH think of themselves as girls.
  - CAH when it occurs in males (XY chromosomes), the result is over-masculinization and premature puberty.
- Mixed gonadal dysgenesis (MGD) is the second most common cause of DSDs.
- Another common DSD is Androgen Insensitivity Syndrome (AIS).
  - This occurs in males (XY chromosomes) who do not respond to testosterone normally.
  - This results in a feminine appearance.
  - There are two types, complete and partial.
  - In Complete Androgen Insensitivity Syndrome (CAIS) the result is a totally feminine appearance, including typical female breast development.
  - Diagnosis in 46,XY phenotypic females with complete androgen insensitivity usually occurs after puberty during an evaluation for primary amenorrhea.
  - In the Partial Androgen Insensitivity Syndrome (PAIS), the genitals can vary from mostly female to almost completely male.
- One of the more unusual DSDs is 5-Alpha Reductase Deficiency (5ARD), popularly known as "Penis at 12."
  - It is caused by a deficiency of the enzyme 5-Alpha Reductase which converts testesterone to dihydrotestesterone in males (XY).
  - Dihyrotestesterone is responsible for the development of the male external genitalia.
- The classic presentation of MIS (Mullerian inhibiting substance) deficiency is a boy with a hernia on one side and an impalpable contralateral gonad. At the time of surgery, a uterus and fallopian tubes are noted along with normal Wolffian structures.
- Clinicians should suspect the possibility of a DSD in patients with both hypospadias and cryptorchidism.
- Infants born with ambiguous genitalia represent a true medical and social emergency.

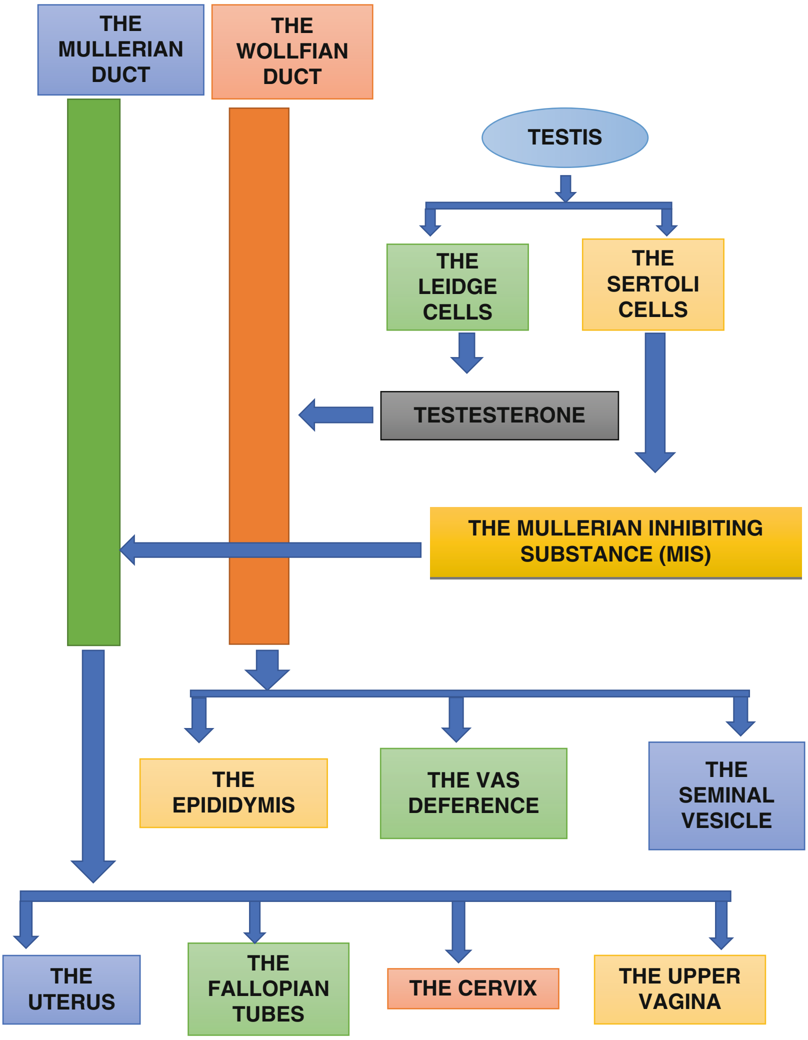
- The management of patients with DSD has also changed over the years.
- In the past, corrective surgeries were often performed in infancy, but in recent years the tendency has been to postpone surgery until the child has expressed a clear gender preference and is old enough to participate actively in decisions about his/her medical treatment.
- The optimal management of patients with DSD must be individualized and multidisciplinary, considering all aspects, including psychological care and full disclosure of alternatives relating to surgery type and timing.
- Modern treatment of infants with ambiguous genitalia involves a team-oriented approach. This gender-assignment team usually involves neonatologists, geneticists, endocrinologists, surgeons, counselors, and ethicists. The goal is to provide appropriate medical support and counseling regarding care and therapy.

31.2 Embryology

- Normal sexual differentiation is based on the genetic sex (XX or XY), which is established at the time of conception.
- Until about 7 weeks of gestation, the fetus is sexually indifferent with two different bipotential gonads and two internally developing wolffian and mullerian ducts.
- Embryologically, there are two undifferentiated bipotential gonads in every embryo.
- These bipotential gonads develops from the urogenital ridge and ultimately develop into either a testis or an ovary.
- In addition to these bipotential gonads, fetuses of both sexes have two sets of internal ducts: the Müllerian ducts and the Wolffian ducts which develop by 6–7 weeks of intra-uterine life.
- At about 7 weeks of gestation:
  - The indifferent gonads and in the presence of a Y chromosome begin to develop into testes.
  - The indifferent gonads and in the absence of a Y chromosome begins to develop into ovaries.
- Thereafter, gonadal differentiation and function determine the final phenotype.
- Many genes are involved in normal sexual differentiation.
  - The sex-determining region on the Y chromosome (SRY) initiates the development of the indifferent gonads into testes.
  - The *SOX9* gene is required for Sertoli-cell differentiation.
  - Steroidogenic factor 1 (SF-1) plays a critical role in steroidogenesis, fertility and male sexual differentiation.
  - *DAX-1* on the X chromosome is upregulated in the ovary and functions as an anti-testis factor.
  - The Wilms tumor (*WT-1*) gene is involved in both gonadal and renal development. Three distinct phenotypes are seen with *WT-1* mutations:
    - The Wilms tumor, aniridia, genitourinary anomalies, and mental retardation syndrome, caused by continuous deletion of the *WT-1* and *PAX-6* genes.
    - Denys–Drash syndrome (a triad of progressive renal disease, 46,XY karyotype with undervirilization, and Wilms tumor. Affected individuals usually have ambiguous genitalia or normal female external genitalia, and streak gonads. Nephrotic syndrome presents within the first 2 years of life and progresses rapidly to end-stage renal failure within a few years.
    - Frasier syndrome (46,XY DSD, gonadal dysgenesis, and renal failure), in which there is an altered ratio of the two splice isoforms of the WT-1 protein. Affected individuals have normal female external genitalia but fail to develop secondary sexual characteristics. Patients are at risk of gonadoblastoma developing in the dysgenetic gonads. Glomerulonephropathy gradually progresses to renal failure in the second or third decade of life.


"Y" CHROMOSOME (SRY)
*"SOX9"*GENE
STEROIDOGENIC FACTOR 1 (SF-1)
THE WILMS TUMOR (*WT-1*) GENE
INDIFFERENT GONAD
TESTIS
NO "Y" CHROMOSOME (SRY)
NO *"SOX9"* GENE
NO STEROIDOGENIC FACTOR 1 (SF-1)
THE WILMS TUMOR (*WT-1*) GENE
DAX-1 ON THE X CHROMOSOME
INDIFFERENT GONAD
OVARY

- Embryologically, two pairs of ducts are present in each fetus whether a male or female:
  - The Wolffian ducts
  - The Müllerian ducts
- In males (XY):
  - The indifferent gonads develop into testes.
  - The testis has two types of cells:
    - The Sertoli cells
    - The Leydig cells
  - The testicular Sertoli cells begin secreting Müllerian-inhibiting substance (MIS) in the seventh week.
  - The MIS acts only locally (paracrine) to induce ipsilateral Müllerian duct regression.
  - The Leydig cells begin producing testosterone through stimulation via placental human chorionic gonadotrophin (hCG).
  - Testosterone acts both locally (paracrine) and systemically (endocrine) to stabilize the Wolffian duct, and promotes the development of the epididymis, the vas deferens and the seminal vesicle.
  - The Wolffian duct leads to the development of:
    - The epididymis
    - The vas deference
  - The seminal vesicle
- In females (XX):
- The lack of MIS permits Müllerian duct maturation into Fallopian tubes, uterus, cervix and upper vagina.
  - The lack testesterone leads to Wolffian duct regression.
  - The Müllerian duct leads to the development of:
    - The uterus
    - The Fallopian tubes
    - The cervix
    - The upper vagina
- The testosterone produced by testicular Leydig cells undergoes peripheral conversion to dihydrotestosterone, under the effect of the enzyme 5α-reductase.
- Dihydrotestosterone is important for the development of the external genitalia in males.
- It induces posterior fusion of the genital folds and growth of the genital tubercle into a phallic structure.
- The development of male external genitalia is complete by 12–16 weeks.
- Subsequent phallic growth is a result of fetal pituitary luteinizing hormone stimulation of testicular Leydig cell testosterone production.


THE MULLERIAN DUCT
THE WOLFFIAN DUCT
TESTIS
THE LEIDGE CELLS
THE SERTOLI CELLS
TESTESTERONE
THE MULLERIAN INHIBITING SUBSTANCE (MIS)
THE EPIDIDYMIS
THE VAS DEFERENCE
THE SEMINAL VESICLE
THE UTERUS
THE FALLOPIAN TUBES
THE CERVIX
THE UPPER VAGINA

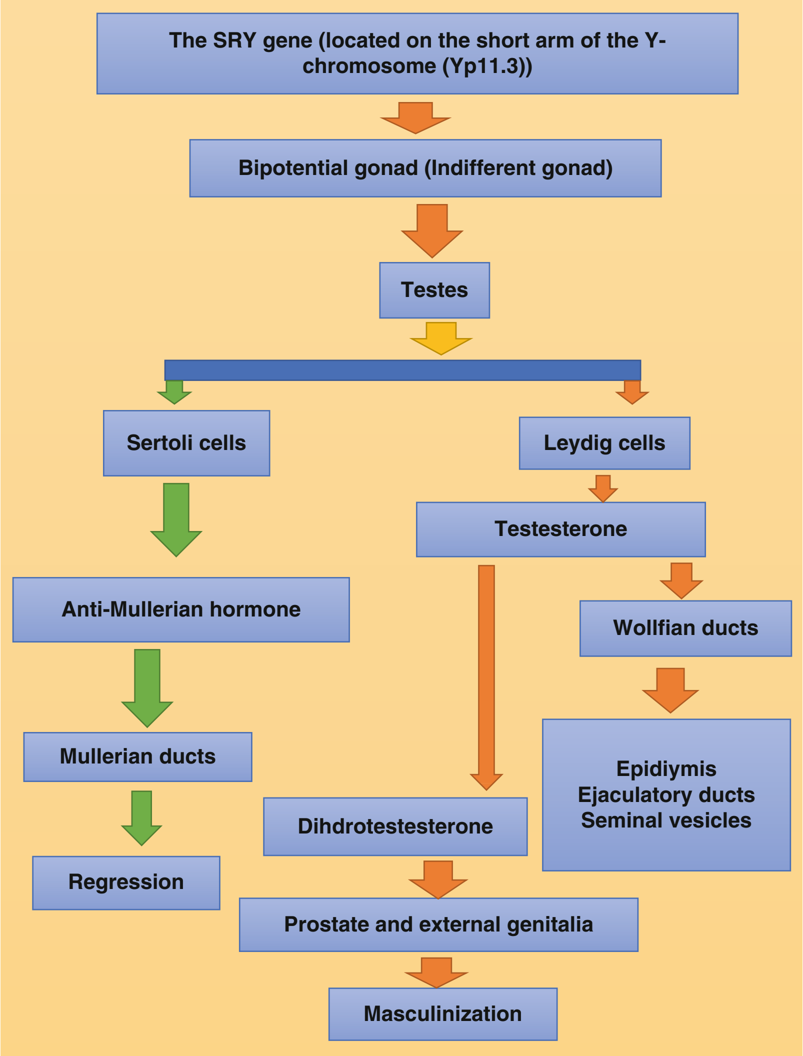
- In females, the non-hormone-dependent separation of the vagina and the urethra is complete by 12 weeks.
- Excess androgen exposure before this separation can cause labial fusion and development of a phallic urethra or urogenital sinus, but later exposure causes only clitoral enlargement and scrotalization of the labial folds.
- Psychosexual development:
  - Psychosexual development has three main components:
- Gender identity:
  - This signifies the child's self-recognition as a boy or a girl, and usually starts at 3 years of age.
- Gender role:
  - This refers to sex-typical behaviors such as toy preferences and physical aggression.
- Sexual orientation:
  - This refers to the direction(s) of sexual interest (heterosexual, bisexual, and homosexual).

  - Many factors affect psychosexual development, e.g. exposure to androgens, sex chromosome genes and brain structure, as well as the society and family perspectives.
  - Gender dysphoria indicates unhappiness with the assigned sex and it results from an inconsistency between the assignment and the inherent identity later in life.
  - Although gender dissatisfaction occurs more frequently in individuals with DSD than in the general population it cannot be easily predicted from the karyotype, prenatal androgen exposure, degree of genital virilization, or assigned gender.
  - Several factors influence prenatal androgen exposure including the timing, dose and type of androgen exposure, and brain receptor availability, as well as the social environment.
  - The prenatal period is thought to be critical for brain masculinization.
  - Girls with congenital adrenal hyperplasia (CAH) with marked genital virilization play more with boys' toys, and the incidence of homosexuality later in life is higher in this group.
  - Moreover, sex chromosome genes might also influence the brain structure and behavior directly.
  - Individuals with complete androgen-insensitivity syndrome (CAIS) however, do not indicate a behavioral role for Y-chromosome genes.

31.3 Sexual and Gonadal Differentiation

- It is important to know that there three types of sex:
  - Phenotypic sex
  - Genetic (chromosomal) sex
  - Gonadal sex
- Chromosomal sex determines gonadal sex, which determines phenotypic sex.
- The type of gonad present determines the differentiation/regression of the internal ducts (Müllerian and Wolffian ducts) and ultimately determines the phenotypic sex.
- Gender identity is determined not only by the phenotypic appearance of the individual but also by the brain's prenatal and postnatal development as influenced by the environment.
- Early during embryonic development, there are two indifferent or bipotential gonads.
- During the second month of fetal life, the indifferent (Bipotential) gonad is guided to develop into a testis by genetic information present on the short arm of the Y chromosome.
- This is under the influence of the testis-determining factor.
- The testis-determining factor (TDF) is a 35–kilobase pair (kbp) sequence on the 11.3 subband of the Y chromosome.
- This is called the sex-determining region of the Y chromosome (SRY).
- When the SRY is absent or altered, the indifferent gonad develops into an ovary.
- Other genes important to testicular development include:
  - *DAX1* on the X chromosome
  - *SF1* on band 9q33
  - *WT1* on band 11p13
  - *SOX9* on bands 17q24-q25
  - *AMH* on band 19q13.3
- This explain the existence of testicular tissue in patients with 46, XX testicular DSD, in the absence of an obvious Y chromosome or SRY genetic material.
- The indifferent gonad develops into fetal ovaries when the *TDF* gene (or genes) is absent.
- The internal ducts (Müllerian and Wolffian ducts) development results from a paracrine effect from the ipsilateral gonad.

- In the absence of testicular tissue, the fetus internal sex duct and external phenotypic development is that of a female.
- The presence of testicular tissue leads to the production of testosterone and Müllerian-inhibiting substance (MIS) or AMH which are important for development of male internal sex ducts and an external male phenotype.
- Testesterone:
  - Testosterone is produced by testicular Leydig cells and induces the primordial Wolffian (mesonephric) duct to develop into:
    - The epididymis
    - The vas deferens
    - The seminal vesicle
  - A spatial relation is important in the effect of testosterone.
  - Wolffian structures located closest to the source of testosterone undergo the greatest degree of male differentiation.
  - This explains why patients with ovotesticular DSDs often have a degree of Wolffian development near testicular tissue, even when joined with an ovary as an ovotestis.
  - No Wolffian development occurs in association with a streak gonad or a non–testosterone-producing dysgenetic testis.
  - High local testosterone levels (paracrine effect) appear to be necessary for Wolffian duct differentiation because maternal ingestion of androgens does not cause male internal differentiation in a female fetus, nor does this differentiation occur in females with CAH (adrenogenital syndrome).
- MIS (Mullerian inhibiting substance):
  - MIS is produced by the Sertoli cells of the testis.
  - It is important to normal male internal duct development.
  - MIS is a 15-kd protein that is secreted by the testis beginning in the eighth fetal week.
  - It prime role is to repress passive development of the Müllerian ducts:
    - Fallopian tubes
    - Uterus
    - Upper vagina
  - In a normal male fetus with normal testicular function, MIS represses Müllerian duct development, whereas testosterone stimulates Wolffian duct development.
- Local testosterone production appears to enhance the inhibition of Müllerian duct development produced by MIS, whereas estrogens may interfere with MIS action, resulting in a degree of Müllerian duct development.
- This may explain the variable internal sex duct anatomy that occurs in some of the more complex DSDs.
- The external genitalia:
  - The external genitalia of both sexes are identical during the first 7 weeks of gestation.
  - Without the hormonal action of the androgens testosterone and dihydrotestosterone (DHT), external genitalia appear phenotypically female.
  - In the gonadal male, differentiation of the external genitalia is moderated by testosterone.
  - Testosterone is converted to 5-DHT by the action of the enzyme, 5-alpha reductase, which is present within the cytoplasm of cells of the external genitalia and the urogenital sinus.
  - DHT is bound to cytosol androgen receptors within the cytoplasm and is subsequently transported to the nucleus, where it leads to translation and transcription of genetic material.

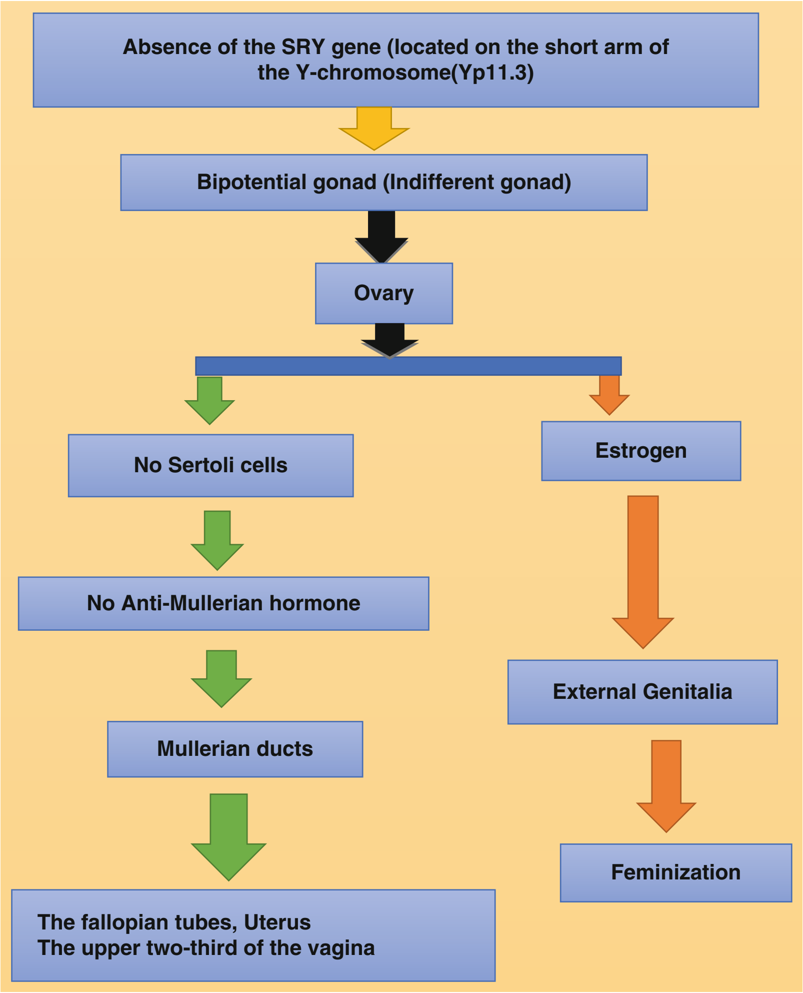

The SRY gene (located on the short arm of the Y-chromosome (Yp11.3))
Bipotential gonad (Indifferent gonad)
Testes
Sertoli cells
Leydig cells
Testesterone
Anti-Mullerian hormone
Wolffian ducts
Mullerian ducts
Epidiymis
Ejaculatory ducts
Seminal vesicles
Dihdrotestesterone
Regression
Prostate and external genitalia
Masculinization

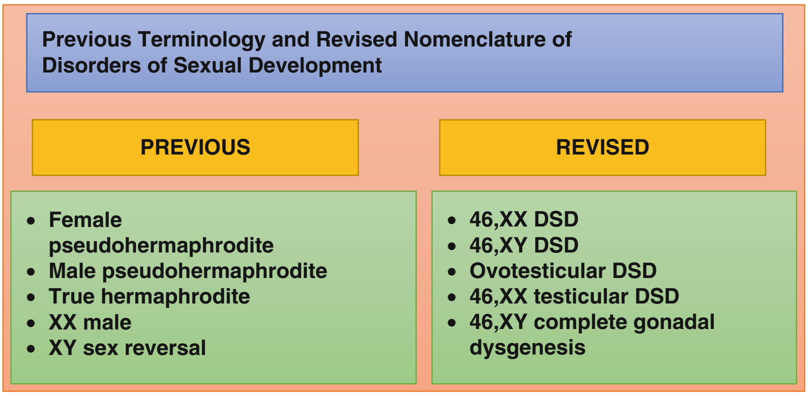
- As a result, these actions lead to normal male external genital development from primordial parts:
  - The scrotum develops from the genital swellings
  - The shaft of the penis develops from the folds
  - The glans penis develops from the tubercle
  - The prostate develops from the urogenital sinus
- Incomplete masculinization occurs when:
  - Testosterone fails to convert to DHT
  - DHT fails to act within the cytoplasm or nucleus of the cells of the external genitalia and urogenital sinus.
- The timing of this testosterone-related developmental change begins at approximately 6 weeks of gestation with a testosterone rise in response to a surge of luteinizing hormone (LH).
- Testosterone levels remain elevated until the 14th week. Most phenotypic differentiation of males occurs during this period.
- After the 14th week, fetal testosterone levels settle at a lower level and are maintained more by maternal stimulation through human chorionic gonadotropin (hCG) than by LH.
- Testosterone's continued action during the latter phases of gestation is responsible for continued growth of the phallus, which is directly responsive to testosterone and to DHT.
- In the gonadal females, differentiation of the external genitalia is moderated by estrogen.

  - Absence of testosterone leads to regression of the Wollfian ducts.
  - Estrogen secreted by the developing ovary leads to the development of the external genitalia of the female.
  - In the female, the genital tubercle becomes the clitoris, the labio-scrotal folds become the labia majora, and the urethral folds become the labia minora.

31.4 Classification

- In the past, several names were used to describe disorders of sexual development.
- These include:
  - Intersex
  - Ambiguous genitalia
  - Hermaphroditism
  - Sex reversal
- In 2006, the Lawson Wilkins Pediatric Endocrine Society (LWPES) and the European Society for Pediatric Endocrinology (ESPE) published proposed changes to the previously used nomenclature and definitions of disorders in which the development of chromosomal, gonadal, or phenotypic sex is atypical.
- The rationale behind these proposals was to change the nomenclature to reflect advances in our understanding of the pathophysiology of these disorders while being sensitive to the needs and concerns of patients affected by them.
- The previous terminology and the revised LWPES-ESPE nomenclature are compared below.
- The LWPES-ESPE terminology mainly reflects the chromosomal sex or the gonadal tissue associated with the disorder.


Absence of the SRY gene (located on the short arm of the Y-chromosome(Yp11.3)
Bipotential gonad (Indifferent gonad)
Ovary
No Sertoli cells
Estrogen
No Anti-Mullerian hormone
External Genitalia
Mullerian ducts
Feminization
The fallopian tubes, Uterus
The upper two-third of the vagina



Previous Terminology and Revised Nomenclature of Disorders of Sexual Development

PREVIOUS	REVISED
• Female pseudohermaphrodite • Male pseudohermaphrodite • True hermaphrodite • XX male • XY sex reversal	• 46,XX DSD • 46,XY DSD • Ovotesticular DSD • 46,XX testicular DSD • 46,XY complete gonadal dysgenesis

- Currently, all these are grouped under one common name, disorders of sexual development, “DSD”.
- This term is broad and includes common entities such as Turner syndrome and Klinefelter syndrome as well as rare disorders such as cloacal exstrophy and aphallia.
- There are several classifications for DSD.
- In the past, intersex disorders were subdivided into three main groups:
  - Those associated with gonadal dysgenesis
  - Those associated with undervirilization of 46,XY individuals
  - Those associated with prenatal virilization of 46,XX individuals
- Another commonly used classification divides intersex disorders into four main groups:
  - Female pseudohermaphroditism
  - Male pseudohermaphroditism
  - True hermaphroditism
  - Mixed gonadal dysgenesis
- The new classification of DSD was proposed by The Lawson Wilkins Pediatric Endocrine Society (LWPES) and the European Society for Paediatric Endocrinoloy (ESPE) group as follows:
  - Sex chromosome DSDs
  - 46,XY DSDs
  - 46,XX DSDs
- Sex chromosome DSDs:
  - This occurs when the number or structure of the sex chromosomes (X, Y chromosomes) is abnormal.
  - The abnormalities include:
    - XX male (46XX)
    - 46 XX/45X
    - 46XY/45X Mixed gonadal dysgenesis
    - 45,XO Turner (Gonadal dysgensis) and variants
    - 47,XXY Klinefelter and variants
    - 45X/46XY mixed gonadal disgenesis (MGD)
    - Chromosomal ovotesticular (True hermaphroditism) DSD “46XX/46XY chimeric type or mosaic type”), (The DSD nomenclature has recently divided “ovotesticular DSD” (formerly true hermaphroditism) into 46,XY ovotesticular DSD, 46,XX ovotesticular DSD, and chromosomal ovotesticular DSD (46,XX/46,XY” chimerism or 45,X/46,XY” mosaic type).
  - Sex chromosome DSD was formerly termed as gonadal dysgenesis.
  - If a testis is poorly formed, it is called a dysgenetic testis, and if an ovary is poorly formed, it is called a streak gonad.
  - A patient with a Y chromosome is at high risk of developing a tumor in a streak or dysgenetic gonad.
  - Klinefelter and Turner syndromes are the most frequently encountered sex chromosomal abnormalities.
  - The most common genotype of Klinefelter syndrome is XXY.

Sex Chromosomes Sexual Disorders of Development (DSD)

- XX male (46XX)
- 46 XX/45X
- 46XY/45X
- 45,XO Turner (Gonadal dysgensis) and variants
- 47,XXY Klinefelter and variants
- 45X/46XY mixed gonadal disgenesis (MGD)
- Chromosomal ovotesticular:
  - 46,XY ovotesticular DSD
  - 46,XX ovotesticular DSD
  - Chromosomal ovotesticular DSD (46,XX/46,XY" chimerism or 45,X/46,XY" mosaic type)

  - More than half of girls with Turner syndrome have chromosomal mosaicism.
  - The clinical manifestations of patients with 45X/46XY MGD, are highly variable, ranging from partial virilization and ambiguous genitalia at birth to a completely normal male or female phenotype.
  - The most common feature of MGD is asymmetric development of the testes, often with a dysgenetic testis on one side and a streak gonad on the other.
  - Asymmetrical external and internal genitalia may also be present.
  - Chromosomal ovotesticular DSD (chimeric type or mosaic type) is associated with ovarian and testicular tissues found in either the same or opposite gonad just as in 46,XX and 46,XY ovotesticular DSD. The genital duct develops according to the ipsilateral gonad.
- 46,XY disorders of sex development (46,XY DSD):
  - Here, the chromosomes are male but the external genitals are either ambiguous or those of a female.
  - The testes may be absent, malformed or normal.
  - In the past, the term "male pseudohermaphrodite" was used to describe patients with 46,XY chromosomes and incompletely masculinized external genitalia.
  - These patients are characterized by ambiguous or female external genitalia, caused by incomplete intrauterine masculinization.
  - Infants with this condition tend to have penoscrotal hypospadias, abnormal development of the testes, and reduced to no sperm production.
  - Some individuals with 46, XY DSD have fully to underdeveloped female reproductive organs (e.g., uterus and fallopian tubes), while others do not.
  - People with 46, XY DSD may be raised as males or females.
  - People with 46, XY DSD are at an increased risk for gonadal tumors and benefit from regular surveillance or surgery to remove abnormally developed gonads.
  - The two main causes of 46,XY DSDs are:
    - Disorders of testicular development
    - Disorders of androgen synthesis/androgen action
  - The spectrum of 46,XY DSDs include:
    - Complete or partial forms of gonadal dysgenesis with or without syndromic phenotype
    - Ovotesticular DSD
    - Testicular regression syndrome
    - Androgen synthesis defects
    - Disorders of androgen action
  - 46,XY partial gonadal dysgenesis is characterized by partial testicular differentiation and ambiguous genitalia.
  - 46,XY complete gonadal dysgenesis (Swyer syndrome) is characterized by:
    - A female phenotype with full development of unambiguous female genitalia
    - Normally developed Müllerian structures
    - Streak gonads
    - These streak gonads should be removed due to their association with gonadoblastoma.
    - These patients usually present because of delayed puberty.
  - Patients with agonadism (vanishing testicular syndrome, testicular regression

    syndrome) are boys with normal male genitalia.
  - This indicates that these patients must have had testicular function in the fetal period followed by bilateral anorchia.
  - Androgen synthesis defect can be secondary to:
    - Leydig cell aplasia/hypoplasia, due to abnormalities in hCG/LH receptor
    - Testesterone biosynthesis defects:
      - STAR deficiency
      - P450scc deficiency
      - 3-b hydroxysteroid dehydrogenase type II deficiency
      - 17a-hydroxylase and 17,20-lyase deficiency
      - Isolated 17,20-lyase deficiency
      - P450 oxidoreductase “POR gene” defect
      - 17b-hydroxysteroid dehydrogenase III deficiency
  - Disorders of Anti-Mullerian Hormone (AMH) and Anti-Mullerian Hormone receptors result in persistent Müllerian duct syndrome (PMDS).
    - PMDS is inherited as a sex-limited autosomal recessive type.
    - It is caused by a mutation in the AMH or AMH-receptor genes.
    - These patients are males and usually present with undescended testis or a hernia.
    - They also have a uterus, Fallopian tube and rudimentary vagina.
  - Disorders of androgen action:
    - 5a-reductase type 2 deficiency
    - Complete/partial forms of androgen insensitivity syndromes
- 46,XX disorders of sex development (46,XX DSD):
  - In this condition, the chromosomes (46,XX) and ovaries are of a female but the external genitals appear to be male (masculinized external genitalia).
  - In the past, this was called female pseudohermaphroditism.
  - 46,XX DSDs can result either from:
    - Disorders of ovarian development.
    - Excess exposure to fetal androgen.
  - SRY positivity; WNT4, RSPO1, b-catenin gene defects; and duplication of SOX9 gene lead to testis-like formation within the ovary (streak gonad, dysgenetic testis or ovotestis) in the 46,XX patients.

46,XY Disorders of Sexual Development (DSD)

- 46,XY disorders of sexual development can be caused by:
  - Defects in testicular development
  - Defects in testosterone biosynthesis
  - Defects in testosterone action
  - Defects in anti-Mullerian hormone
- Defects in testicular development:
  - 46,XY complete gonadal dysgenesis (Swyer syndrome)
  - 46,XY partial gonadal dysgenesis (Denys-Drash syndrome, Frasier syndrome)
  - Ovotesticular DSD
  - Testicular regression syndrome (vanishing testes syndrome)
  - Leydig cell aplasia/hypoplasia
- Defects in testosterone biosynthesis:
  - STAR deficiency
  - P450scc
  - 3-b hydroxysteroid dehydrogenase deficiency
  - 17a-hydoxlase and 17,20-lyase deficiency
  - Isolated 17,20-lyase deficiency
  - P450 oxidoreductase “POR” gene defect
  - 17b-hydroxysteroid dehydrogenase III deficiency
  - POR gene abnormality (defective 17,20-lyase activity of P450c17)
- Defects in anti-Mullerian hormone:
  - Persistent Mullerian duct syndrome
- Defects in testosterone action:
  - 5a-reductase type 2 deficiency
  - Complete androgen insensitivity syndromes
  - Partial androgen insensitivity syndromes

  - In ovotesticular DSDs, the most common karyotype is 46,XX followed by 46,XX/46,XY chimerism or mosaicism, and 46,XY.
  - Most 46,XX ovotesticular DSDs are SRY-negative, and the genes responsible have not yet been identified.
  - The main cause of a virilized females with two ovaries, XX karyotype and ambiguous genitalia is excess exposure to testosterone before birth.
    - The excess testosterone exposure is usually of fetal origin
    - Rarely this excess is of maternal origin.
  - The majority of virilized 46,XX infants will have congenital adrenal hyperplasia (CAH) secondary to enzyme deficiency:
    - 21a-hydroxylase deficiency (most common)
    - 11b- hydroxylase deficiency
    - 3b-hydroxysteroid dehydrogenase deficiency (rare)
  - A combined P450c17 and P450c21 deficiency is a very rare variant of CAH.
  - Cytochrome POR is a protein that transfers electrons from NADPH to all microsomal cytochrome P450 enzymes and three steroidogenic enzymes, namely:
    - P450c17 (17a-hydroxylase/17,20 lyase)
    - P450c21 (21-hydroxylase)
    - P450aro (aromatase)
  - Mutations of POR gene cause disordered steroidogenesis with prenatal virilization.
  - Causes of fetal androgen excess in XX infants are rare and include:
    - Maternal androgen ingestion
    - Maternal virilizing disease
    - Fetoplacental aromatase deficiency
    - Virilizing luteoma of pregnancy
    - Glucocorticoid receptor mutation
  - Aromatase enzyme deficiency:
    - This is rare type of enzyme deficiency.
    - Aromatase is the enzyme that catalyzes conversion of androgens into estrogens.
    - As a result of this enzyme deficiency, DHEA produced by the fetal adrenal glands cannot be converted to estrogen by the placenta, and is converted to testosterone peripherally.
    - This results in virilization of both fetus and mother.
    - These patients can present during childhood and adolescence with cystic ovaries and delayed bone maturation. They may also present at puberty with:
      - Primary amenorrhea
      - Failure of breast development
      - Virilization
      - Hypergonadotrophic hypogonadism

- Another way of classifying disorders of sexual development is as follows:
  - Disorders of sex chromosomes
  - Disorders of gonads
  - Disorders of phenotype

46,XX Disorders of Sexual Development (DSD)

- 46,XX disorders of sex development:
  - Disorders of ovarian development
  - Excess exposure to fetal androgen
- Disorders of ovarian development.
  - Ovotesticular DSD
  - Gonadal dysgenesis
  - Vaginal atresia
  - Cloacal exstrophy
- Excess exposure to fetal androgen
  - Congenital adrenal hyperplasia
    - 21a-hydroxylase deficiency (most common)
    - 11b- hydroxylase deficiency
    - 3b-hydroxysteroid dehydrogenase deficiency (rare).
  - P450c17 (17a-hydroxylase/17,20 lyase) deficiency
  - P450c21 (21-hydroxylase) deficiency
  - P450aro (aromatase) deficiency
  - Maternal excess of androgens:
    - Maternal androgen ingestion during pregnancy
    - Fetoplacental aromatase deficiency
    - Virilizing luteoma of pregnancy

A comprehensive classification (Aaronson's classification) based on gonadal histology

1. Ovarian DSD:
   - The gonads are composed of normal ovarian stroma with numerous follicles.
2. Ovotesticular DSD:
   - The gonads are essentially composed of both ovarian and testicular tissues, either in two separate gonads or within a single gonad.
   - At the least, a well-defined ovarian follicle should be seen to diagnose the ovarian element.
   - The testicular component comprises architecturally ordered tubules, although the intervening stroma may be more abundant than normal.
3. Testicular DSD:
   - The seminiferous tubules are normal, although Leydig cells might be prominent.
4. Dysgenetic DSD:
   - The tubules are disordered, often sparse, and the stromal tissue is abundant.
   - These gonads have a strong propensity to undergo malignant degeneration.

- Disorders of sex chromosomes (Chromosomal sex):
  - This occurs when the number or structure of the sex chromosomes (X, Y chromosomes) is abnormal.
  - The abnormalities include:
    - Klinefelter syndrome 47 XXY
    - XX male (46XX)
    - Turner syndrome (gonadal dysgenesis) 45 XO
    - 46 XX/45X

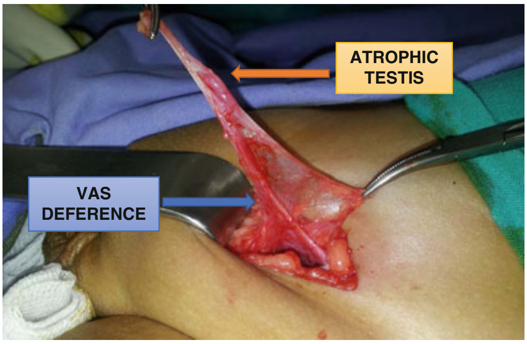


Fig. 31.10 A clinical intraoperative photograph showing atrophic testis. Note the presence of a vas

    - Mixed gonadal dysgenesis 46XY/45X
    - True hermaphroditism 46 XX, 46XY or mosaics
- Disorders of gonads (Gonadal sex) (Figs. 31.10 and 31.11):
  - Disorders of gonadal sex result when chromosomal sex is normal but differentiation of the gonads is abnormal.
  - The abnormalities include:
    - Pure gonadal dysgenesis
    - Dysgenetic testes
    - Absent testes
- Disorders of phenotype (Phenotypic sex):
  - In these disorders the gonads and sex chromosomes are normal but with abnormal urogenital tract.
  - The abnormalities include:
    - Female pseudohermaphrodite
    - Congenital adrenal hyperplasia
    - Nonadrenal female pseudohermaphroditism
    - Developmental disorders of mullerian duct
    - Male pseudohermaphrodite
    - Abnormalities in androgen synthesis
    - Abnormalities in androgen action
    - Persistent mullerian duct synd
    - Developmental defects of male genitalia

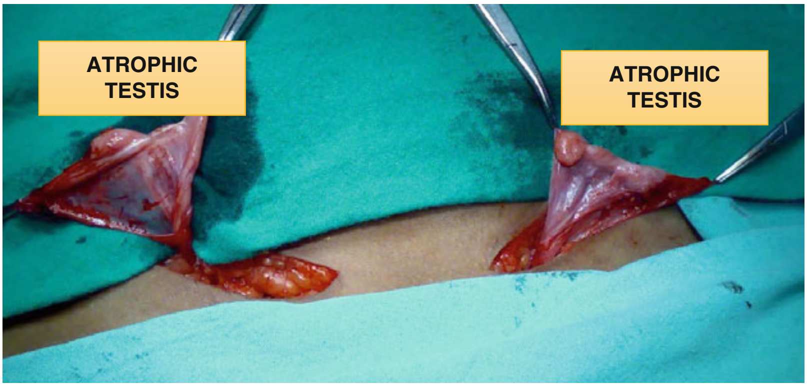


Fig. 31.11 Intraoperative photograph showing bilateral atrophic testes

31.5 Evaluation of a Newborn with DSD

- The evaluation, diagnostic approach and management of a newborn with DSD involves a multidisciplinary team approach.
- This team include:
  - Neonatologists
  - Geneticists/genetic counselor
  - Pediatric endocrinologists
  - Pediatric surgeons
  - Social worker
  - Pediatric urologist
  - Psychologist
- The most common disorder of sexual development (DSD), congenital adrenal hyperplasia (CAH), results in virilization of a 46,XX female.
- The clinician's challenge is to distinguish CAH from other less common causes of ambiguous genitalia.

Classification of DSD

1. Sex chromosome DSD
   - 45,X0/46,XY Mixed gonadal dysgenesis (MGD)
   - 45,X0/46,XY Partial gonadal dysgenesis
   - 46,XX/XY or 45,X0/46,XY Ovotesticular DSD
   - 45,X0 or 45,X0/46,XY (Turner's syndrome)
   - Seminiferous tubule dysgenesis: Klinefelter's syndrome (47,XXY)
2. 46,XX (DSD)
   - Androgen excess: (60–70 %)
     - CAH (vast majority)
       - 21-Hydroxylase deficiency (95 %)
       - 11β-Hydroxylase deficiency (5 %)
       - 3β-Hydroxysteroid dehydrogenase deficiency
     - Maternal androgens (very rare)
       - Endogenous: Virilising tumours in the mother
       - Exogenous (very rare)
   - Disorders of ovarian development
     - Ovotesticular DSD
     - 46,XX testicular DSD (SRY translocation)
     - Pure gonadal dysgenesis (e.g. SOX9 duplication
   - Meyer–Rokitansky syndrome (Müllerian aplasia)
3. 46,XY DSD
   - Disorders of testicular development
     - Gonadal dysgenesis (Swyer syndrome = Pure, DAX-1 Duplication. SF-1 mutation)
     - Ovotesticular DSD
     - Bilateral vanishing testis/testicular regression syndromes

- Disorders of androgen synthesis or action
    - Leydig cell agenesis, unresponsiveness
    - Enzyme deficiency
        - StAR deficiency (lipoid adrenal hyperplasia
        - 3β-Hydroxysteroid dehydrogenase deficiency
        - 17α-Hydroxylase deficiency
        - 17,20-Lyase deficiency
        - 17β-Hydroxysteroid oxidoreductase deficiency
        - 5α-Reductase deficiency
- Disorders of androgen-dependent target tissue
    - CAIS (testicular feminisation)
    - PAIS
- Persistent Müllerian duct syndrome

4. Others: Severe hypospadias and cryptorchidism, penile agenesis and cloacal exstrophy

- A detailed family history is essential; the following considerations should be kept in mind:
    - A family history of genital ambiguity, infertility, or unexpected changes at puberty may suggest a genetically transmitted trait.
    - Recessive traits tend to occur in siblings, whereas X-linked abnormalities tend to appear in males who are scattered sporadically across the family history.
    - A history of early death of infants in a family may suggest a previously missed adrenogenital deficiency
    - Maternal drug ingestion is important, particularly during the first trimester, when virilization may be produced exogenously in a gonadal female.
    - Although extremely rare, a history of maternal virilization may suggest an androgen-producing maternal tumor (arrhenoblastoma)
- Sex assignment:
    - It is important not to assign a sex immediately and delay it till after full evaluation.
    - During the evaluation stage, the newborn is referred to as "baby," not boy or girl.
    - The family should be encouraged to delay naming the baby until the sex has been assigned.
- There are other factors that must be taken in consideration during this process including:
    - The social and cultural background.
    - Expectations of the parents.
    - Religious factors.
- The parents are also involved, educated and should participate in the process and should understand that a children with a DSD can live normal live and function well in society.
- Although different DSDs may present with similar findings on physical examination, there are certain clinical and laboratory aspects that are important and will help define the type of DSD.
- It is important to rule out a malformation syndromes that may present as ambiguous genitalia (Fig. 31.12).
- Clinical evaluation of the gonads and external genitalia is very important:
    - It is important to note the size and degree of differentiation of the phallus.
    - Note the phallus length:
        - A normal-term male penis is 3.5 ± 0.7 cm.
        - A length of less than 2.0 cm is considered abnormal.
        - A normal-term female clitoris is less than 1.0 cm.
        - Micropenis is thus defined as a stretch penile length of less than 2.0 cm in a term male infant, and clitoromegaly as a clitoris greater than 1.0 cm in a term female. In preterm infant males, the penile length is shorter.
    - Note the position of the urethral meatus:
        - Hypospadias associated with bifid scrotum or undescended testis suggests a DSD (Figs. 31.13 and 31.14).
        - If the urethral opening is at the base of the phallus, it could be a urogenital sinus in a virilized female.
    - Labioscrotal folds may be separated or be fused at the midline, giving an appearance of a scrotum.

  - Newborns with 46XX DSD due to CAH may have hyperpigmented labioscrotal folds.
  - The anogenital ratio:
    - This is the distance between the anus and posterior fourchette divided by the distance between the anus and base of the clitoris/phallus.
    - A ratio greater than 0.5 suggests virilization.
    - In a fully virilized male the ratio is 1.0.
  - Documentation of palpable gonads is also important:
    - Although ovotestes have been reported to descend completely into the bottom of labioscrotal folds, in most patients, only testicular components descends fully.
    - If clinical evaluation reveals palpable gonads in the inguinal area, the diagnoses of pure gonadal dysgenesis can be eliminated.
    - Impalpable gonads, even in an apparently fully virilized infant, should raise the possibility of a severely virilized 46XX DSD patient with CAH.
    - The presence of two palpable gonads strongly favors the diagnosis of a 46XY DSD.
    - The presence of only one palpable gonad suggests the diagnosis of mixed gonadal dysgenesis, although it does not rule out a 46 XX ovotesticular DSD.

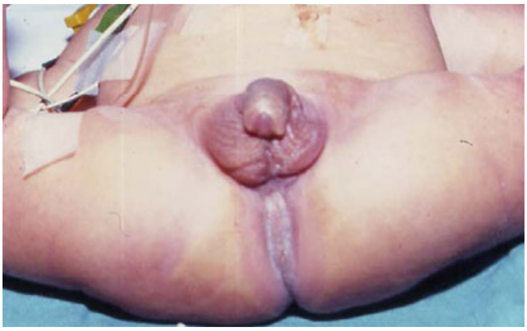
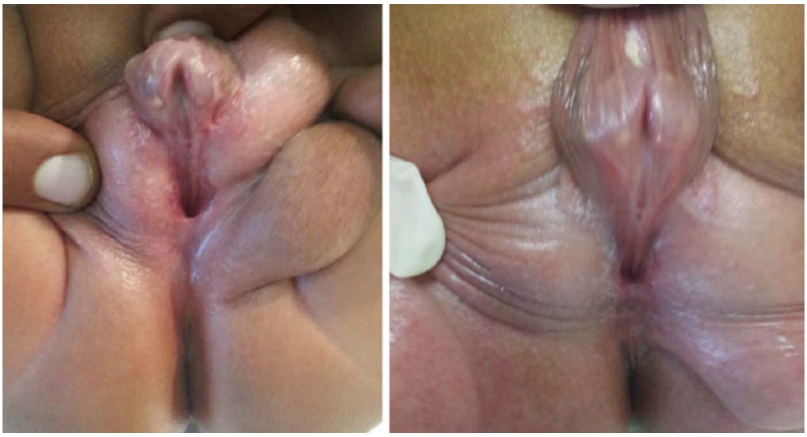


Fig. 31.12 A clinical photograph of a newborn with DSD. Note also the associated anorectal agenesis

31.6 Diagnosis and Investigations

- The optimal care of patients with DSD requires a multidisciplinary team and begins in the newborn period.
- Some cases of DSD are obvious at birth while others are diagnosed during childhood or remain undiagnosed until a child reaches puberty.
- The investigations depend on the suspected type of DSD.
- The diagnostic evaluation of DSD includes:
  - A complete CBC and electrolytes
  - Hormone measurements
  - Hormone stimulation tests
  - Diagnostic radiological evaluations
    - Ultrasonography shows the presence or absence of Müllerian/Wolfian structures and can locate the gonads and their echo texture.



Figs. 31.13 and 3.14 Clinical photographs showing severe degrees of hypospadias. Note the bifid scrotum also

  - Ultrasonography also can identify associated malformations such as renal abnormalities.
- Cytogenetic and molecular studies
- Endoscopic, laparoscopic and gonadal biopsy
- Retrograde genitogram is performed for the anatomical outlining of the urogenital sinus and for localizing the position and entry of the urethra and vagina into the sinus.
- The genetic evaluation includes:
  - Chromosomal analysis (Karyotype)
  - FISH
  - Specific molecular studies to screen the presence of mutations or gene dosage imbalance (AR, SRY, SF1, WT1, CYP21, SOX9, DAX-1, 17b hydroxysteroid dehydrogenase, 5a-reductase-2, and others). These are not readily avaliable.
  - Current molecular diagnosis is limited by cost, accessibility, and quality control.
- Common findings suggesting DSD are:
  - A male appearance with associated abnormalities of genitalia including:
    - Severe hypospadias with bifid scrotum
    - Undescended testis/testes with hypospadias
    - Bilateral non-palpable testes
    - Micropenis with chordee.
  - A female appearance with associated abnormalities of genitalia including:
    - Enlarged clitoris
    - Posterior labial fusion
    - An inguinal/labial mass.
- The location of the gonads and presence or absence of a uterus, will provide a provisional clinical diagnosis.
  - If no gonads are palpable:
    - 46,XX DSD (with two ovaries) is the most commonly seen.
    - MGD.
    - The presence of a uterus and absence of palpable gonads in a virilized female primarily suggest a clinical diagnosis of 21-hydroxylase deficiency.
    - MGD, ovotesticular, and 46,XY DSD remain as diagnostic possibilities.
  - If two gonads are palpable:
    - 46,XY DSD and ovotesticular DSD are the most likely diagnoses.
    - Symmetrical external genitalia, with or without palpable gonads, and an absent uterus suggest an undervirilized XY male.
    - The presence of a uterus and asymmetric external genitalia and palpable gonad(s) suggest gonadal dysgenesis with Y and ovotesticular DSD.
    - A gonadal biopsy is required to classify the type of gonadal dysgenesis and ovotesticular DSD, to assess gonadal chromosomal mosaicism and to detect the presence of a gonadal tumor.
- Hormone measurements should include hCG and ACTH stimulation tests to assess testicular and adrenal steroid biosynthesis.
- The endocrine evaluation of patients with 46,XY DSDs and sex chromosome DSDs include assessment of testicular function by basal measurement of LH, FSH, inhibin B, Testesterone, Dihyrotestesterone (DHT), Anti-Mullerian hormone (AMH), and DHEAS.
- In patients with Testesterone synthesis defects, neonatal and post pubertal diagnosis is made based on basal steroid levels.
- Testesterone stimulation test:
  - The stimulation of Testesterone production by hCG is used to determine abnormalities in Testesterone biosynthesis and also to document the presence of functioning testicular tissue.
  - Testosterone and DHT should be measured at baseline and 72 h after hCG stimulation.
  - The increase in the level of Testesterone should be at least threefold.
  - A failure to respond to hCG in combination with elevated LH/FSH levels and low/undetectable value of AMH is

  consistent with anorchia or gonadal dysgenesis.
  - Androgen insensitivity should be considered in individuals with a 46,XY karyotype and with normal Testesterone biosynthesis.
  - Patients with 5a-reductase deficiency have normal Testesterone levels, low or normal DHT levels and a high Testesterone/DHT ratio after hCG stimulation test.
- The testosterone level can help to determine whether the DSD is due to a lack of androgen or cortisone synthesis or rather due to a receptor defect.
- An elevated level of 17-hydroxyprogesterone is diagnostic of CAH.
- Determining the levels of 11-deoxycortisol and deoxycorticosterone will help to make a differential diagnosis between 21-hydroxylase and 11β-hydroxylase deficiencies. If the levels are elevated, a diagnosis of 11β-hydroxylase deficiency could be made, whereas low levels confirm 21-hydroxylase deficiency.
- The diagnosis of 17bHydroxysteroid dehydrogenase deficiency is made when a 10- to 15-fold elevation is observed in the ratio of A/T.
- Inhibin B and AMH are useful markers for the presence of Sertoli cells and their assessment could help in the diagnosis of testis determination disorders.
- Serum AMH level:
  - This is indicative of the presence of testicular tissue.
  - In boys with bilateral cryptorchidism, serum AMH correlate with the presence of testicular tissue.
  - Undetectable values are highly suggestive of absence of testicular tissue.
  - In XY patients, AMH is low in those with DSD secondary to abnormal testicular determination (including complete and partial gonadal dysgenesis).
  - AMH will be normal or elevated in patients with impaired Testesterone secretion.
  - AMH level will be elevated during the first year of life and at puberty in those with androgen insensitivity.
  - In 46,XX patients with DSDs, a high serum AMH level is indicative of the presence of testicular tissue.
- The diagnosis of 21-hydroxylase deficiency in 46,XX DSDs with two ovaries depends on:
  - The detection of elevated 17-OHP levels either as a basal measurement or after a short ACTH stimulation test.
  - High concentration of 11-deoxycortisol and deoxycortisol (DOC) with low levels of plasma renin activity (PRA).
  - This will help differentiate 11- hydroxylase from 21-hydroxylase deficiency.
- Study of androgen target cells:
  - Defects in peripheral sensitivity to androgens may be responsible for genital ambiguity in male individuals with partial androgen insensitivity.
  - Androgen receptor activity can be determined in fibroblasts grown from a genital skin biopsy sample.
  - 5-alpha reductase activity can be determined by this method.
- Chromosomal characteristics, gonadal histology and presence or absence uterus are taken into consideration in the classification of DSDs.
- In rare cases in which a definite diagnosis cannot be determined and in infants with intra-abdominal or nonpalpable testes in whom DSDs are considered, open or laparoscopic exploration with biopsy of the gonads could become necessary.
- In some cases, the differential diagnosis of DSD depends on the interpretation of the histologic features of the gonads.
- Infants with intra-abdominal or nonpalpable testes in whom the precise diagnosis is unavailable with karyotyping and serum study will require an open or laparoscopic exploration with bilateral deep longitudinal gonadal biopsies for histologic evaluation, which will determine the presence of ovotestes, streak gonads, or dysgenetic testes, thereby confirming the diagnosis.

31.7 Management of Patients with DSD

- The management of patients with DSD depends on the underlying cause.
- Supplemental hormone therapy may be given if gonadal function is compromised.
- In a virilized female, the surgical management is feminizing genitoplasty and this includes vaginoplasty and clitoroplasty.
- Undervirilized males typically have hypospadias and this is corrected with urethroplasty.
- Gender reassignment may be considered in patients with 46XY males and inadequate external genitalia.
- Sex assignment and therapy:
  - There are several factors which must be considered during sex assignment, including:
    1. The phenotype
    2. The appearance of the genitals
    3. The surgical options
    4. The need for future hormonal replacement therapy
    5. The potential for future fertility
    6. The culture and preferences of the family
    7. The effect of high levels of testosterone exposure on the brain development
- Sex assignment also depends on the type of DSD (46XX DSD, 46XY DSD or chromosomal DSD)
- 46 xx chromosomes:
  - Congenital adrenal hyperplasia:
    - These patients are usually assigned a female sex.
    - Their fertility is preserved.
    - These patients are given hydrocortisone to replace cortisol, and, if there is associated salt wasting, fludrocortisone is given to replace aldosterone.
    - Surgical treatment is required to correct the external genitalia. This should be done early and includes:
      - Clitoroplasty.
      - Vaginoplasty
- 46 XY chromosomes:
  - Testosterone biosynthesis defects
    - These patients are assigned a male sex.
    - Fertility is preserved.
    - Some of these patients have deficiencies of glucocorticoids and/or mineralocorticoids and these are treated with glucocorticoids and/or mineralocorticoids.
    - Patients with hypospadias require urethroplasty.
    - Testosterone replacement may be required at puberty, particularly if testosterone levels remain low.
  - 5-alpha-reductase deficiency
    - These patients are assigned a male sex.
    - Fertility is preserved.
    - Patients with hypospadias require urethroplasty.
    - These patients do not typically require hormonal replacement and the rise in testosterone levels at the onset of puberty is sufficient to induce development of secondary sexual characteristics.
  - Partial androgen resistance
    - Most of these patients are raised as males and fertility is preserved.
    - Some patients with severe partial androgen resistance may be raised as females, as adequate virilization at puberty may not be possible.
    - If the patient is raised as a male, early surgical correction of hypospadias is recommended.
    - Testosterone replacement may be required at puberty, particularly if testosterone levels remain low.
    - If the patient is raised as a female:
      - Early vaginoplasty is recommended.
      - Clitoroplasty in those with severe virilization.
      - These patients require gonadectomy before puberty to prevent virilization at puberty and also malignant transformation.
      - Estrogen supplements are required at puberty to allow development of secondary sexual development.
  - Gonadal dysgenesis
    - The sex assignment in these patients depends on several factors including:
      - The likelihood of fertility.
      - The genital appearance.

    - The size of the phallus.
    - The presumed testicular function in puberty which is based on hormonal tests and gonadal development.
  - If the patient is raised as a female:
    - Early vaginoplasy is recommended.
    - Clitoroplasty in those with severe virilization.
    - Gonadectomy before puberty to prevent virilization at puberty and possible malignant transformation.
    - Estrogen supplements at puberty to allow development of secondary sexual development.
  - If the patient is raised as a male:
    - Early surgical correction of hypospadias is recommended.
    - Testosterone replacement may be required at puberty, particularly if testosterone levels remain low.
- 45 X/ 46 XY mixed gonadal digenesis
  - Sex assignment is more complex in these patients.
  - If fertility is likely to be maintained, then sex assignment is best chosen to be consistent with fertility.
  - Other factors that must be taken in consideration including:
    - The genital appearance
    - The size of the phallus.
    - The presumed testicular function in puberty based on hormonal tests and gonadal development.
  - The risk of gonadal malignancy is highest in mixed gonadal dysgenesis in which there is a Y chromosomal and in those with an intra-abdominal testis.
  - In children assigned a male sex, hypospadias is corrected with urethroplasty.
  - A streak ovary, if present, should be removed.
  - Testosterone replacement may be required at puberty, particularly if testosterone levels remain low.
  - In children assigned a female sex, the following corrective procedures are required:
    - Early vaginoplasty.
    - Clitoroplasty in those with severe virilization.
    - Gonadectomy should be performed early to prevent malignancy and avoid any risk of virilization.
    - Estrogen supplements at puberty to allow development of secondary sexual development.
    - Some of these patients have Mullerian structures (uterus) and need treatment with cyclic progesterone once breakthrough bleeding occurs.

31.8 Surgical Corrections of DSD

- The aims of corrective surgery for patients with DSD are:
  - To make ambiguous external genitalia compatible with assigned gender
  - To prevent urinary obstruction or infections
  - To preserve sexual and reproductive potentials
  - To maximize anatomy to enhance sexual function
- Surgical corrections are aimed at:
  - The gonads
  - The external
  - The presence of a urogenital sinus
- In general, it is recommended that the decision about reconstructive genital surgery should be made by the parents and, when possible, the patient. This should be taken under the counseling and advice of the treating medical team.
- It is important to inform the parents that a functional outcome is more important than a cosmetic outcome.
- It is also important to inform the patients and parents not to have unrealistic expectations about penile reconstruction.
- Genital reconstructive surgery in infancy that makes an appearance consistent with the gender of rearing is of significant psychological support to the family.
- Others feel that corrective surgery is not urgent and that it is more appropriate to delay surgery until a patient is old enough to be informed fully and to participate in decision making.

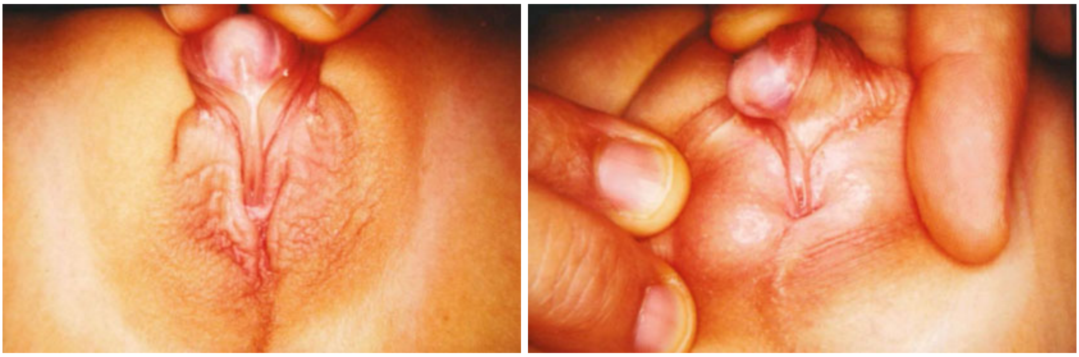
- In a virilized female, the surgical procedure is termed feminizing genitoplasty and includes vaginoplasty and clitoroplasty. The optimal timing of feminizing genitoplasty is still controversial.
- The American Academy of Pediatrics guidelines on the timing of genital surgery recommend feminizing genitoplasty between 2 and 6 months of age and many pediatric urologists also recommend early feminizing genitoplasty.
- Feminizing genitoplasty for the infants who are to be raised as females includes:
  - Removing the corporal bodies
  - Creating a normal-looking introitus and labia minora and majora
  - Vaginoplasty to provide an adequate vaginal opening
- Masculine reconstruction may include:
  - Orchidopexy
  - Repair of hypospadias
  - Excision of retained Müllerian duct structures when present
- Clitroplasty:
  - Clitoroplasty should be considered only in cases of severe virilization.
  - It should be performed combined with repair of the common urogenital sinus.
  - Until the 1960s, the principal surgical procedure for clitoromegaly was clitoridectomy.
  - Clitoridectomy results in a near normal looking female perineum but it will affect the orgasmic function and erectile sensation.
  - Clitoridectomy is currently contraindicated.
  - The preferred procedure is clitoral reduction. This spares the neurovascular bundle which is important for the preservations of intact orgasmic function and erectile sensation.
- Vaginoplasty:
  - Some authors prefer to correct the external genitalia in a single-stage procedure in the newborn period to take advantage of all native genital tissue and to avoid subsequent scarring.
  - This is also advantageous to the parents.
  - Others advocate delaying vaginal reconstruction until puberty when vaginal dilatations are more feasible to prevent vaginal stenosis. To prevent stenosis, vaginal dilatation can begin 2 weeks after the operation.
  - Labioplasty is performed at the time of the vaginoplasty and gives the external genitalia a normal female appearance.
  - During clitoroplasty, the remnant skin from the clitoris shaft could be used to make the labia minora and majora.
- Phaloplasty:
  - Currently, there is no tissue available to increase the size of an underdeveloped phallus.
  - In patients with DSD associated with hypospadias, the complexity of this procedure must be discussed with the parents during the initial counseling.
  - The standard surgical repair include:
    - Increase penile size and length with topical or injectable testosterone.
    - Chordee correction
    - Repair of hypospadias
- Gonadectomy:
  - There is controversy regarding the timing of gonadectomy.
  - It is recommended that gonadectomy should be performed soon after diagnosis because estrogen-replacement therapy could be started.
  - Others prefer delayed gonadectomy.
  - The advantages of late gonadectomy include breast development and avoidance of poor adolescent compliance with estrogen-replacement therapy.
  - Germ cell malignancy only occurs in patients with DSD who have Y-chromosomal material (GBY region).
  - Testes in patients with 46,XY gonadal dysgenesis who are raised as a female should be removed to prevent testicular malignancy.
  - In patients with androgen biosynthetic defects raised who are raised as females, gonadectomy should be performed before puberty.
  - A scrotal testis in patients with gonadal dysgenesis is at risk for malignancy. The

  current recommendations are to perform testicular biopsy at puberty to diagnose carcinoma in situ or undifferentiated intratubular germ cell neoplasia, which are premalignant lesions. If positive, the option is sperm banking before treatment with local low-dose radiotherapy.
  - In female patients with ovotesticular DSD, the tumor risk is low (<5 %), but removal of the testicular component in early life is recommended to preserve fertility potential.
- Medical and psychotherapy:
  - Hypogonadism is common in patients with:
    - Dysgenetic gonads
    - Defects in sex-steroid biosynthesis
    - Resistance to androgens
  - Hormone-replacement therapy is often required in patients with DSD to:
    - Induce and sustain puberty
    - Induce secondary sexual characteristics
    - Induce pubertal growth spurt
    - Optimize bone mineral accumulation
    - Help with psychosocial maturation
  - Boys with hypogonadism require intramuscular injections of either testosterone cypionate or ethanate for pubertal induction.
  - Other testosterone preparations such as gels and patches are also available.
  - In girls with hypogonadism, estrogen supplementation to induce secondary sexual changes and menstruations is required.
    - Estrogen can be given orally, by injection, or patch.
    - A progestin is usually added after breakthrough bleeding develops or within 1–2 years of continuous estrogen.
  - Psychosocial care should be an integral part of the management of patients with DSD to promote positive adaptation.
    - Families and individuals require ongoing counseling by experienced personnel.
    - Other important resources include access to confidential sexual counseling and support groups.
    - Regular follow-up from infancy to adulthood of sexual, psychological, and social parameters is important.

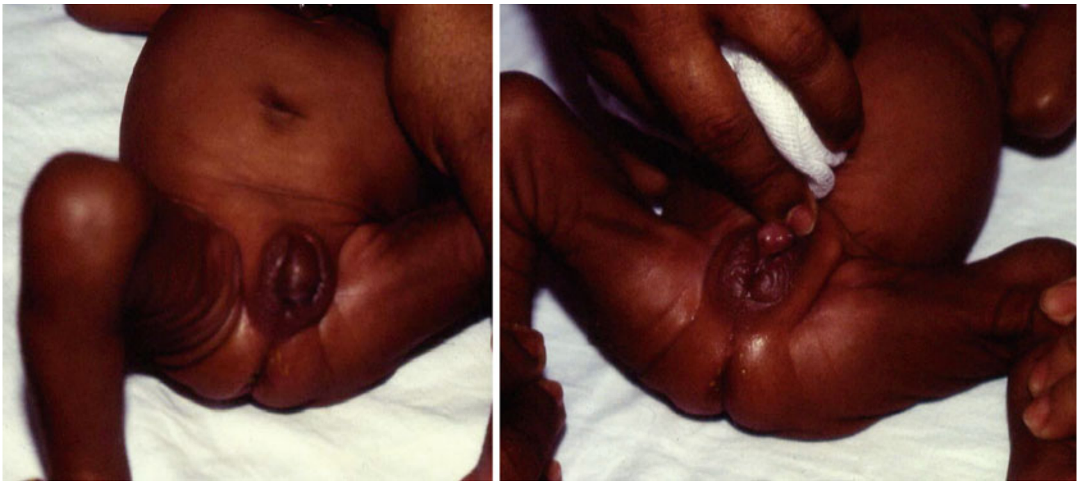
31.9 Congenital Adrenal Hyperplasia (CAH)

- CAH is the most common cause of DSD in the newborn.
- In the past, patients with CAH were called female pseudohermaphrodites.
- CAH accounts for 60–70 % of ambiguous genitalia in a newborn.
- It is characterized by the followings:
  - The gonads are ovaries bilaterally.
  - The Müllerian system develops normally into Fallopian tubes, uterus and upper vagina.
  - The Wolffian system derivatives regresses.
  - The karyotype is 46,XX.
- The basic biochemical defect is an enzymatic block that prevents sufficient cortisol production. Biofeedback via the pituitary gland causes the precursor to accumulate above the block. Clinical manifestation of CAH depends on which enzymatic defect is present.
- The metabolic and biochemical consequences of CAH are variable.
- The majority of CAH cases (95 %) are due to an autosomal recessive deficiency of 21-hydroxylase.
- As a result of this enzyme deficiency, the adrenal gland is unable to form cortisone and the adrenal steroid hormone synthesis is diverted towards the androgen pathway, resulting in virilization.
- In 75 % of the cases, the deficiency affects both cortisone and aldosterone production. This also results in salt loosing.
- If the zona glumerulosa is spared, aldosterone production remains normal and only simple virilization without salt wasting (25 %) results.
- The second most common enzyme deficiency is 11β-hydroxylase.
  - The characteristic feature of this enzyme deficiency is the accumulation of desoxycorticosterone that causes salt retention and hypertension.
- Virilization of the external genitalia varies from minimal phallic enlargement to almost complete masculinization.

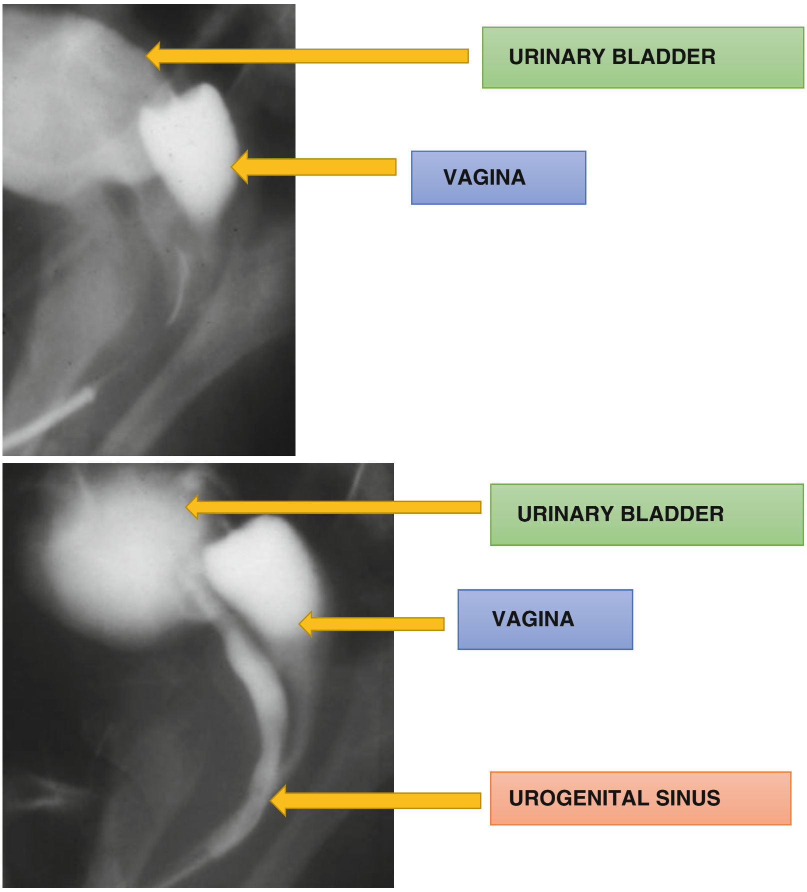
- Because of the andrenocorticotropic hormone drive there is hyperpigmentation of the external genitalia and nipples.
- These patients are raised as females especially those with mild to moderate virilization.
- Fertility is normally expected in these patients.
- A prenatal diagnosis of CAH in high-risk families is possible via:
  - Determination of an elevated 17-hydroxyprogesterone in amniotic fluid
  - Human leukocyte antigen genotyping of chorionic villus samples
- However, the diagnosis cannot be confirmed before the initial development of the external genitalia.
- Medical treatment with life-long cortisone replacement after birth is mandatory.
- Mineralocorticoteroids are indicated in those with salt wasting CAH.
- The incidence of CAH to be 1 case per 15,000 live births.
- Frequency was highest in neonates of European Jewish, Hispanic, Slavic, or Italian descent.
- Male infants with this syndrome may be phenotypically normal, and the diagnosis may be missed.
- CAH may result from several metabolic defects, one of which is 21-hydroxylase deficiency.
- In 90 % of patients with CAH, the block is at the 21-hydroxylation enzyme. This leads to a mineralocorticoid deficiency and a buildup of androgenic byproducts, which causes masculinization of a female fetus.
- The result is a female infant with varying degrees of virilization.
- Biochemically, 75 % of patients have salt-wasting nephropathy. Before this condition was commonly recognized, as many as one third of patients presented with evidence of vascular collapse.
- The 21-hydroxylase defect is inherited as an autosomal recessive trait closely linked to the human leukocyte antigen (HLA) locus on chromosome 6. The transmitted trait may have two varieties, which helps account for the clinical heterogenicity seen in patients with salt-wasting nephropathy.
- Diagnosis is confirmed by an elevated serum level of 17-OHP.
  - Reference range newborn cord blood levels of 17-OHP can be as high as 900–5,000 ng/dL, but the serum level rapidly decreases by the second or third day of life.
  - A repeat elevated serum value exceeding 500 ng/dL at this point makes the diagnosis highly likely.
  - It should be kept in mind that 17-OHP levels may be markedly elevated in the 11-hydroxylase form of CAH, as well as in the rare child with the 3-beta-hydroxysteroid dehydrogenase form.
- CAH presents a spectrum of abnormalities, including (Figs. 31.15, 31.16, 31.17, and 31.18):
  - The degree of phallic enlargement
  - The extent of urethral folds fusion
  - The size and level of entry of the vagina into the urogenital sinus
- The level of entry of the vaginal opening into the urogenital sinus is divided into two types (Figs. 31.19, 31.20, 31.21, and 31.22):



Figs. 31.15 and 3.16 Clinical photographs showing congenital adrenal hyperplasia. Note the degree of phallic enlargement and the extent of urethral folds fusion



Figs. 31.17 and 3.18 Clinical photographs of a patient with CAH showing virilization of external genitalia


URINARY BLADDER
VAGINA
URINARY BLADDER
VAGINA
UROGENITAL SINUS

Figs. 31.19 and 3.20 Genitograms showing the level of entry of the vaginal opening into the urogenital sinus. This shows a low level of insertion

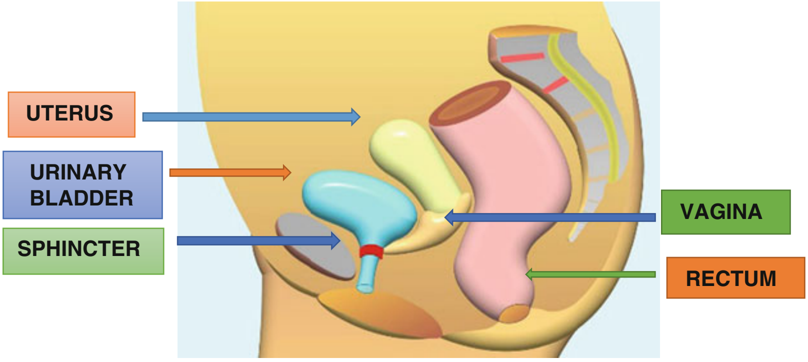


Fig. 31.21 Diagrammatic representation of urogenital sinus showing high insertion of the vaginal opening into the urogenital sinus. Note the point of entry above the sphincter

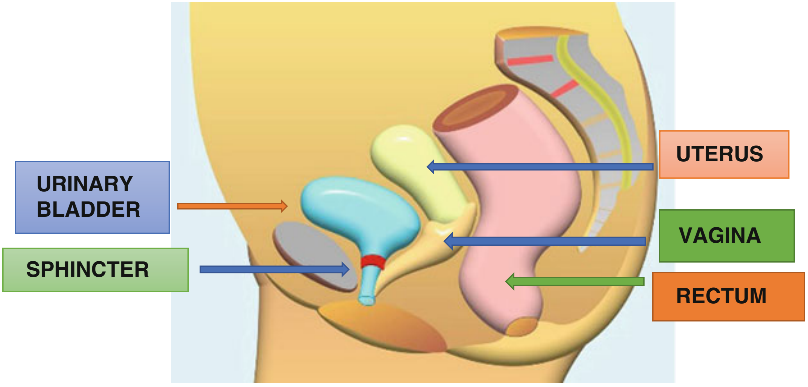
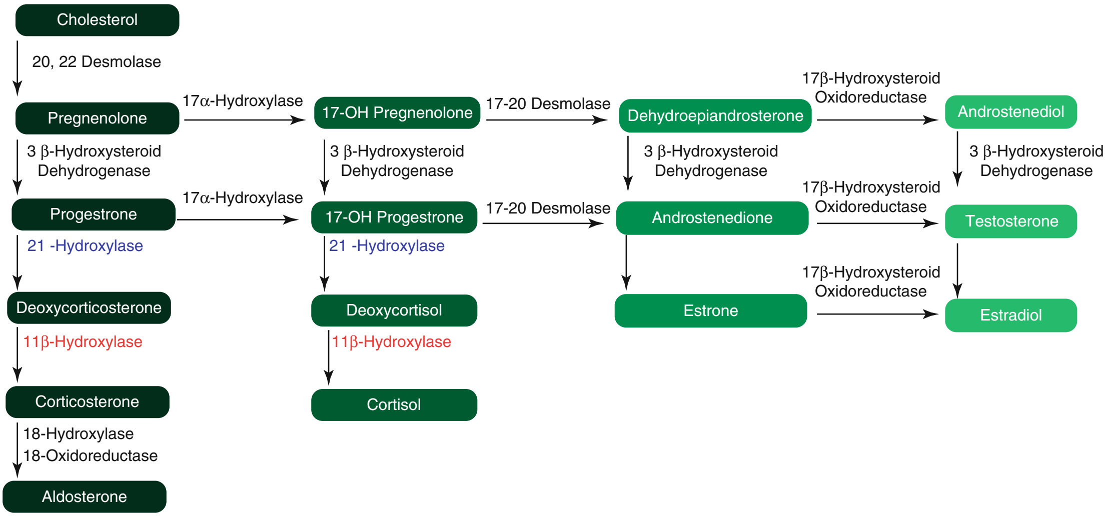


Fig. 31.22 Diagrammatic representation of urogenital sinus showing low insertion of the vaginal opening into the urogenital sinus. Note the point of entry below the sphincter

  - Below the urethral sphincter
  - Above the urethral sphincter
- The internal Müllerian structures are well developed in these patients and females with this condition are usually fertile with the ability to become pregnant and give birth.
- There is a salt-losing variety of CAH and this is fatal in infants if left untreated as it causes hypotension which can cause vascular collapse and death.
- Causes of CAH:
  - CAH is commonly caused by enzyme deficiencies in the sex hormones pathway as follows:
    - 21-Hydroxylase deficiency
    - 11-Hydroxylase deficiency
    - 3-Beta-hydroxysteroid dehydrogenase deficiency
  - Rarely, CAH is caused by maternal androgens
  - 21-Hydroxylase deficiency:
    - This is the commonest cause seen in 90 % of patients with CAH.
    - This leads to a mineralocorticosteroid deficiency.
    - As a result of this, there is accumulation of androgenic byproducts, which causes masculinization of a female external genitalia.
    - The end result is a female infant with varying degrees of virilization.
    - A large number of these patients (75 % of patients) have also salt-wasting. This is a serious condition which must be recognized and treated to avoid vascular collapse.

    - The 21-hydroxylase deficiency is hereditary inherited as an autosomal recessive trait.
    - The transmitted trait may have two varieties, which explains the clinical heterogenecity seen in patients with salt-wasting nephropathy.
    - CAH can be diagnosed prenatally by demonstrating an elevated amniotic fluid level of 17-hydroxyprogesterone (17-OHP) during the second trimester or by HLA typing of amniotic cells.
    - CAH is commonly diagnosed in newborns during evaluation of a 46XX newborn with ambiguous genitalia and the diagnosis is confirmed by demonstrating an elevated serum level of 17-hydroxyprogesterone.
    - 17-Hydroxyprogesterone levels may be elevated also in the 11-hydroxylase deficiency form of CAH, as well as in the rare type seen in those with the 3-beta-hydroxysteroid dehydrogenase deficiency.
- – 11-Hydroxylase deficiency:
    - Another cause of CAH is 11-hydroxylase deficiency.
    - Patients who have CAH with 11-hydroxylase block accumulate deoxycorticosterone (DOC) and 11-deoxycortisol.
    - This form of the syndrome exhibits salt retention and hypertension because DOC is a potent mineralocorticoid.
    - The diagnosis can be confirmed by a steroid screen of the serum.
    - CAH secondary to 11-hydroxylase deficiency leads to accumulation deoxycorticosterone (DOC) and 11-deoxycortisol.
    - CAH secondary to 11-hydroxylase deficiency should be suspected in a 46XX child with ambiguous genitalia in whom:
        - – The 17-Hydroxyprogesterone level is mildly elevated.
        - – There is accumulation of deoxycorticosterone and 11-deoxycortisol.
- – 3-Beta-hydroxysteroid dehydrogenase deficiency:
    - A less frequently seen version of CAH is caused by 3-beta-hydroxysteroid dehydrogenase deficiency.
    - This version causes less severe virilization of a female infant than the virilization caused by 21-hydroxylase or 11-hydroxylase deficiency.
    - The buildup of pregneninolone, which is subject to hepatic conversion into testosterone, produces the virilization.
    - These patients can present with a salt-losing crisis caused by deficient mineralocorticoid production, similar to that occurring with 21-hydroxylase deficiency.
    - The diagnosis can be confirmed by identifying an elevated serum level of dehydroepiandrosterone or its sulfate metabolite.
    - It should be kept in mind that 3-beta-hydroxysteroid dehydrogenase deficiency is the only common form of CAH that can also cause ambiguity in the genetic male. This ambiguity occurs because the enzyme defect is present in both the adrenal glands and the testes, leading to inadequate production of testosterone in utero.
    - 3-beta-hydroxysteroid dehydrogenase deficiency is the only common form of CAH that can also cause ambiguous genitalia in the genetic male.
    - This ambiguous genitalia occurs because this enzyme defect is present in both the adrenal glands and the testes, leading to inadequate production of testosterone in utero.


Cholesterol
20, 22 Desmolase
Pregnenolone
17α-Hydroxylase
17-OH Pregnenolone
17-20 Desmolase
Dehydroepiandrosterone
17β-Hydroxysteroid Oxidoreductase
Androstenediol
3 β-Hydroxysteroid Dehydrogenase
3 β-Hydroxysteroid Dehydrogenase
3 β-Hydroxysteroid Dehydrogenase
3 β-Hydroxysteroid Dehydrogenase
Progestrone
17α-Hydroxylase
17-OH Progestrone
17-20 Desmolase
Androstenedione
17β-Hydroxysteroid Oxidoreductase
Testosterone
21 -Hydroxylase
21 -Hydroxylase
17β-Hydroxysteroid Oxidoreductase
Deoxycorticosterone
Deoxycortisol
Estrone
Estradiol
11β-Hydroxylase
11β-Hydroxylase
Corticosterone
Cortisol
18-Hydroxylase
18-Oxidoreductase
Aldosterone

- Maternal androgens:
  - Although rare, 46,XX DSDs may be drug-induced.
  - Virilization of a female fetus may occur if progestational agents or androgens are used during the first trimester of pregnancy.
    - After the first trimester, these drugs cause only phallic enlargement without labioscrotal fusion.
    - The incriminated drugs were formerly administered to avoid spontaneous miscarriages in patients who had a history of habitual abortion.
  - Endocrine abnormality in the mother as a source of virilizing hormones is even rarer because these abnormalities, if initially present, usually prevent development of a pregnancy.
  - Extremely rare, various functional ovarian tumors have caused virilization of a female fetus.
  - These tumors include:
    - Arrhenoblastomas
    - Krukenberg tumors
    - Luteomas
    - Lipoid tumors of the ovary
    - Stromal cell tumors of the ovary

Causes of Congenital Adrenal Hyperplasia

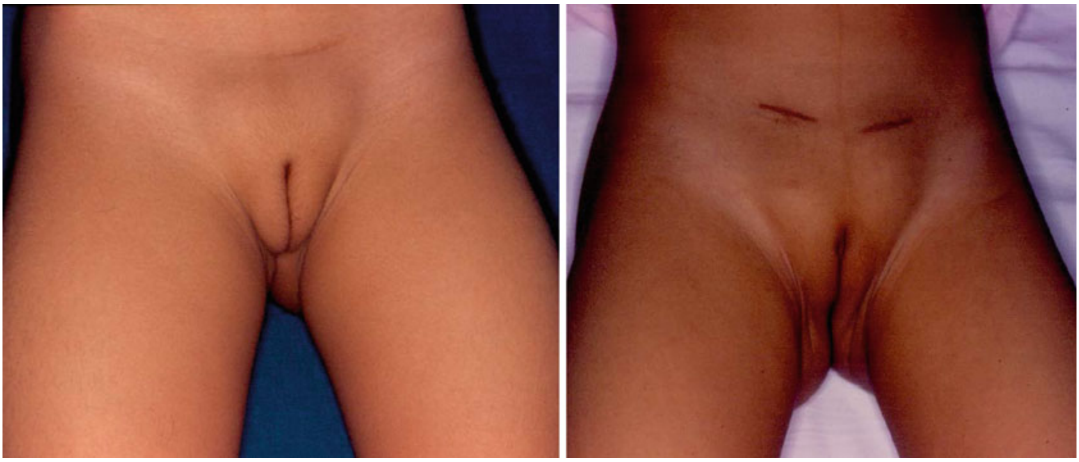
- Enzyme deficiency:
  - 21-Hydroxylase deficiency
  - 11-Hydroxylase deficiency
  - 3-Beta-hydroxysteroid dehydrogenase deficiency
- Maternal androgens:
  - Drug-induced (Progestational agents or Androgens)
  - Functional ovarian tumors
    - Arrhenoblastomas
    - Krukenberg tumors
    - Luteomas
    - Lipoid tumors of the ovary
    - Stromal cell tumors of the ovary

- Management:
  - These patients are treated early.
  - They should receive hormone replacement with corticosteroids.
  - Those with salt-losing CAH must be recognized and treated with replacement therapy including corticosteroids and minerlocorticoids.
  - The surgical management is variable depending on the extent of virilization and include:

  - Clitroplasty
  - Vaginoplasty depending on the level of entry of the vaginal opening into the urogenital sinus.
  - Labioplasty

31.10 Androgen Insensitivity Syndrome (Testicular Feminization Syndrome)

- Androgen insensitivity syndrome affects males.
- There are two types of androgen insensitivity syndrome:
  - Complete androgen insensitivity syndrome
  - Partial androgen insensitivity syndrome
- Partial androgen insensitivity syndrome results in ambiguous genitalia and there is no consensus whether to raise a child with this syndrome as a male or female.
- Complete androgen insensitivity syndrome causes a genetically male to have an incompletely developed and often blind ended vagina, clitoris and breasts.
- Patients with complete androgen insensitivity syndrome are raised as females.
- Patients with complete androgen insensitivity syndrome do not have a uterus or ovaries and are infertile.
- Syndromes of androgen insensitivity involve a failure of the end organ (external genitalia and prostate) in a 46,XY gonadal male fetus to respond to appropriately produced levels of dihydrotestosterone (DHT), resulting in testicular feminization.
- Currently, the basic pathophysiology of the lack of androgen effect on the genitalia is understood more fully.
  - Some patients are receptor-negative; their cytosol receptors cannot bind DHT.
  - Another variant is receptor-positive, in which receptors apparently permit DHT binding, but DHT does not lead to normal differentiation toward the male phenotype.
  - Assays of genital skin fibroblasts elucidate the difference between receptor-negative and receptor-positive types.
- Inheritance of this syndrome appears to be X-linked.
- Complete androgen insensitivity presents in infancy only if the child has a shallow blind-ending vagina, reflecting the lack of internal müllerian development expected in an XY patient whose testes manufacture MIS at reference range levels.
- Inguinal hernias are common in testicular feminization, and an occasional case is detected during inguinal herniorrhaphy when a gonad is present in the hernia and a fallopian tube cannot be seen (Figs. 31.23, 31.24, 31.25, 31.26, and 31.27).
- Failure to identify an internal müllerian structure in a phenotypic female with an inguinal hernia should always raise the possibility of testicular feminization.
- If not detected in this fashion, diagnosis usually is not made until puberty, when the patient presents with amenorrhea.
- Although these characteristics are not noted early in life, these girls exhibit a body hair deficiency as they age, and their breasts, although well formed, characteristically are deficient in stroma.
- Despite a 46,XY karyotype and gonads with the typical appearance of testes (perhaps altered similarly to those with cryptorchidism), a feminine gender assignment is unquestionable because of the completely feminine phenotype and because end-organ failure prevents endocrinologically produced masculinization.
- Confirmation of the diagnosis is crucial because the syndrome is associated with a significant incidence of gonadal malignancies.
- Malignant tumors are termed germinomas or, more properly, seminomas because the tumors arise in a testis.
  - The youngest reported age of occurrence of malignant tumor was 14 years.
  - Overall frequency of gonadal malignancies is approximately 6 %, with incidence rising to more than 30 % by age 50 years.



Figs. 31.23 and 31.24 Clinical photographs showing two female patients who had unilateral and bilateral inguinal herniotomy and found to have complete androgen insensitivity syndrome

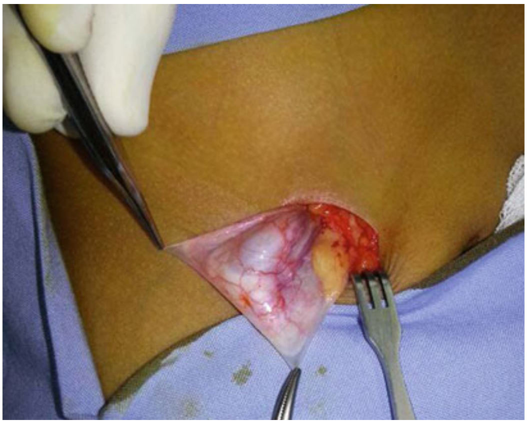
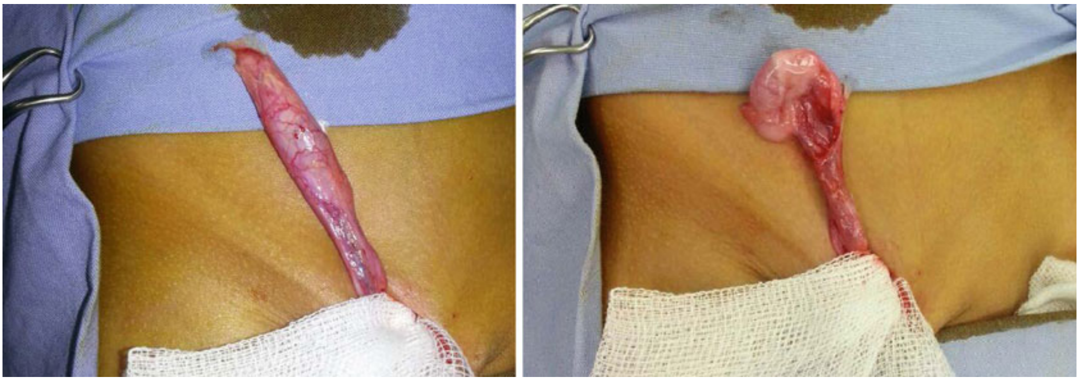


Fig. 31.25 A clinical photograph showing a female patient who was found to have complete androgen insensitivity syndrome at the time of herniotomy. Note the normal looking testis in the hernial sac

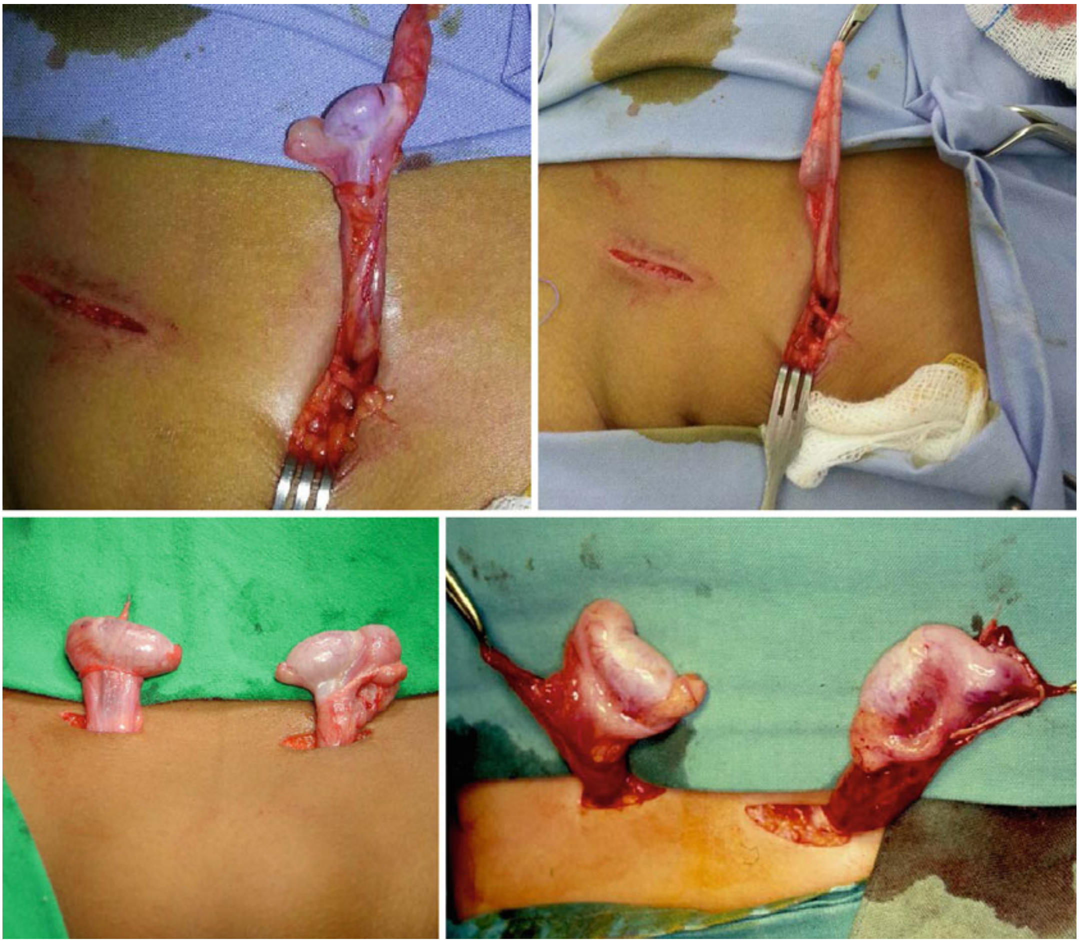
  - Sertoli cell and Leydig cell tumors have been reported also.
  - Tubular cell adenomas, also fairly frequent, have a potential for malignancy because neoplastic transformation has been reported.
- Disagreement exists on the best timing for gonadectomy.
  - There are those who advocate delayed gonad removal after puberty.
  - Others advocate early gonadectomy because morbidity is minimal in a young child.
- Pubertal changes are induced easily with hormone replacement, a requirement for all patients following gonadectomy.
- Although a vaginoplasty later may be required, many of these girls have an adequate vagina, requiring no therapy or possibly only vaginal dilation.
- Complete androgen insensitivity syndrome:
  - This is seen in a 46XY male.
  - CAIS occurs at a frequency of 1 in 20,000 to 1 in 64,000 male births.
  - It results from failure of the end organ (external genitalia and prostate) to respond appropriately to dihydrotesteterone (DHT).
  - There are two subtypes of complete androgen insensitivity syndrome:
    - Receptor-negative type: These patients are receptor negative and the main problem is that their cytosol receptors cannot bind DHT.
    - Receptor-positive type: These patients are receptor positive but in spite of DHT binding to its receptors it does not lead to normal differentiation of the external genitalia toward the male phenotype.
  - This can be diagnosed based on assays of genital skin fibroblasts.
  - Complete androgen insensitivity syndrome is inherited as X-linked.
  - The gonads are symmetrical and exclusively testicular tissue (seminiferous



Figs. 31.26 and 31.27 Clinical photographs showing a hernia sac containing a normal looking testis in a female patient who was found to have complete androgen insensitivity syndrome at the time of herniotomy. Note the normal looking testis

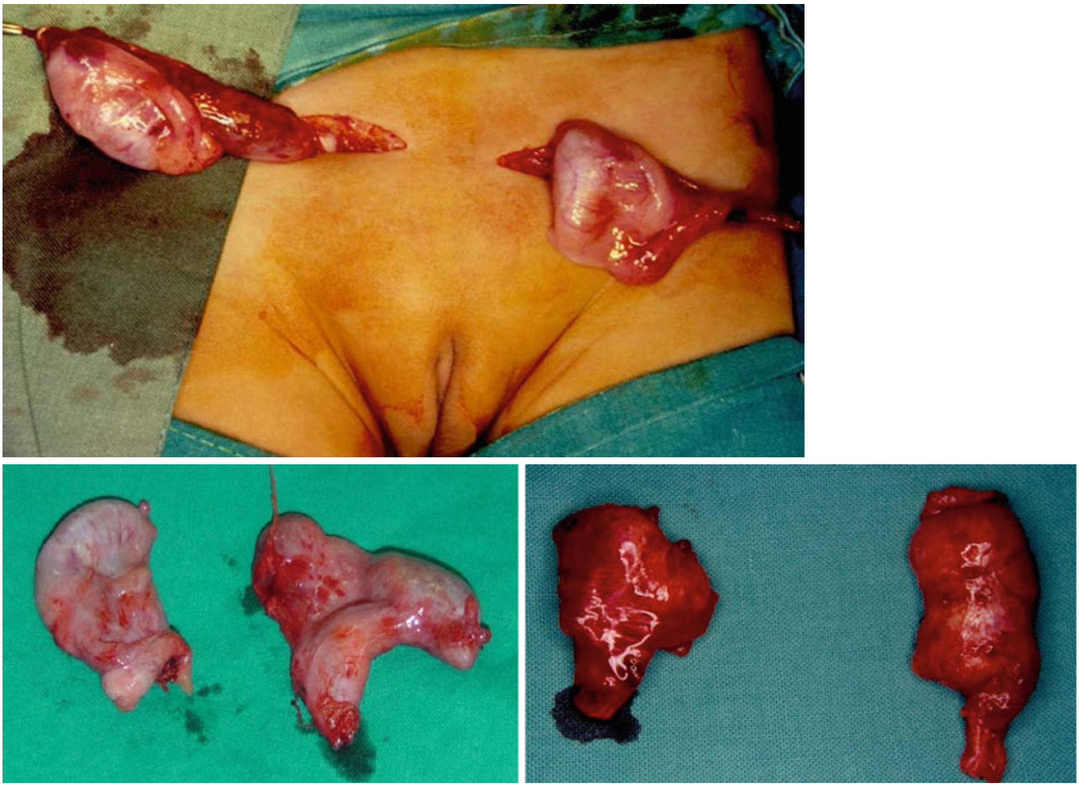
tubules with no spermatogenesis and increased numbers of Leydig cells).

- The Wolffian ducts develop in half of these cases, while all Müllerian structures regress.
- Phenotypically, patients are normal, tall and hairless females with feminine external genitalia and a very short and shallow utricle.
- At the time of puberty, normal breasts develop due to peripheral conversion of testosterone to estrogen.
- Axillary and pubic hair is absent or scanty, with slight vulval hair development.
- Amenorrhoea is the rule.
- A large number of patients with complete androgen insensitivity syndrome present with inguinal hernias and sometimes the diagnosis is made during inguinal herniorrhaphy when a gonad is present in the hernial sac.
- Failure to identify an internal Müllerian structure in a phenotypic female with an inguinal hernia should always raise the possibility of testicular feminization syndrome (Figs. 31.28, 31.29, 31.30, 31.31, 31.32, 31.33 and 31.34).
- The other presentation of complete androgen insensitivity syndrome is at puberty, when the patient presents with amenorrhea.
- Despite a 46XY karyotype and gonads with the typical appearance of testes, these patients are raised as females because of the completely feminine phenotype.
- It is important to establish the diagnosis in these patients because of the associated risk of gonadal malignancies.
- The diagnosis after puberty can be made by the presence of a male androgen and gonadotrophin profile in a phenotypically female patient.
- A prepubertal diagnosis is more difficult and requires an hCG stimulation test and PCR characterization of the androgen-receptor gene in DNA obtained from a venous blood sample.
- The gonads are at low risk of malignancy because of the cryptorchidism (2 %).
- As the risk starts after puberty a gonadectomy at puberty allows the spontaneous onset of puberty to be followed by estrogen therapy.
- A prepubertal gonadectomy can be done if the condition is causing discomfort or hernia formation, or if the gene mutation has not been characterized, to avoid virilization at the time of puberty.
- Gonadoblastomas are the commonest malignant tumors in these patients.
- Other tumors include: Sertoli cell and Leydig cell tumors and tubular cell adenomas.
- The management of these patients include and early or delayed gonadectomy.
- The timing for gonadectomy is still controversial.
- There are those who recommend gonadectomy after puberty.

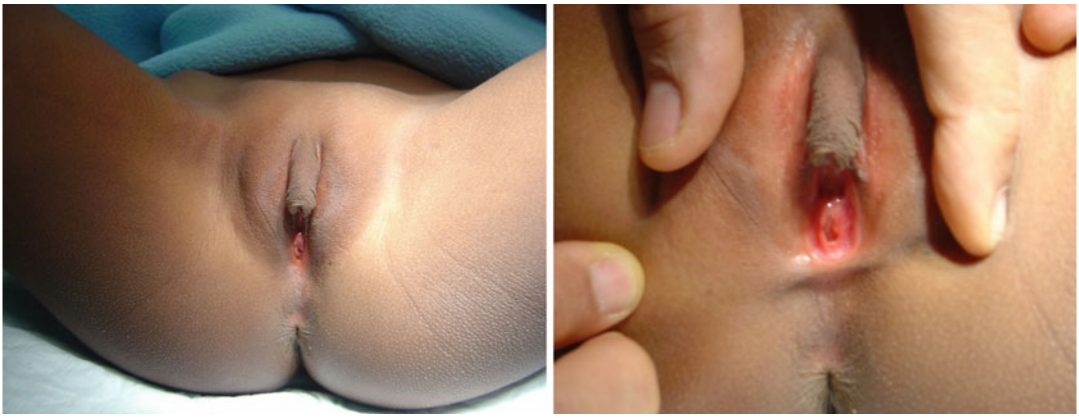


Figs. 31.28, 31.29, 31.30, and 31.31 Clinical photographs showing complete androgen insensitivity syndrome with normal testes discovered at the time of herniotomy. The timing for gonadectomy is still controversial

  - In contrast, others recommend early gonadectomy because morbidity is minimal in a young child. This also avoid the potential risk of loss of some of these patients during follow-ups.
  - Hormone replacement is important in these patients at puberty to induce secondary female sexual characteristics.
  - These patients may have a small vagina and a vaginoplasty may be required later in life.
  - Others have an adequate vagina, requiring no vaginoplasty or possibly only vaginal dilation.
- Partial (incomplete) androgen insensitivity syndrome (PAIS) (Figs. 31.35 and 31.36):
  - An incomplete form of androgen insensitivity also occurs.
  - In the Partial Androgen Insensitivity Syndrome (PAIS), the genitals can vary from mostly female to almost completely male.
  - Some people with PAIS think of themselves as girls/women, others regard themselves as boys/men, and some consider themselves mixed-gender.
  - These patients demonstrate a spectrum of external genitalia ranging from:
    - Very feminine (Lubs syndrome)
    - Increasingly masculine (Gilbert-Dreyfus syndrome)
    - Most masculine (Reifenstein syndrome)
  - They may present only with micropenis or cliteromegaly and causes a problem with gender assignment.

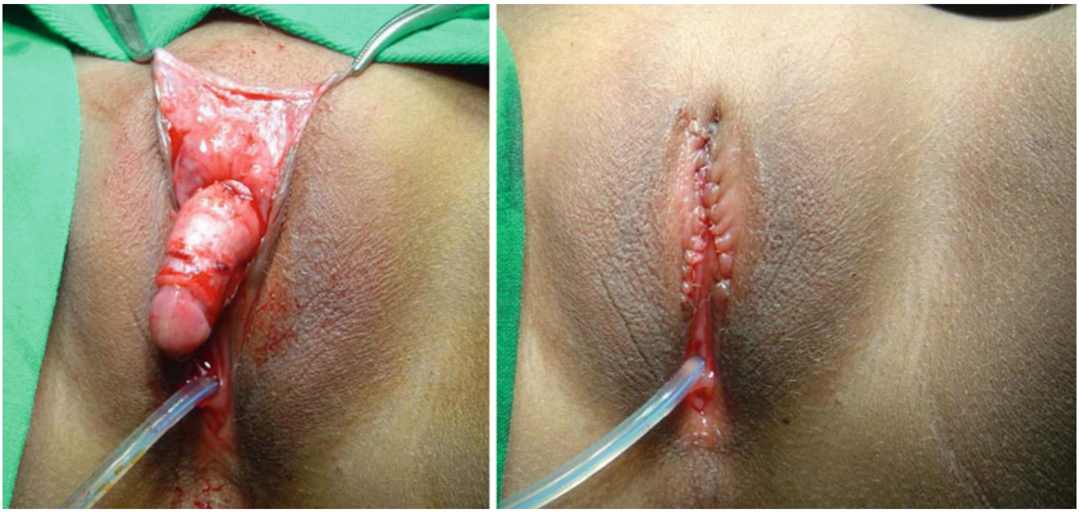


Figs. 31.32, 31.33, and 31.34 Clinical intraoperative photographs showing a patient with testicular feminizing syndrome with bilateral intraabdominal undescended testes found at the time of inguinal herniotomy. Note also the bilateral gonadectomy done early for two patients with testicular feminizing syndromes



Figs. 31.35 and 31.36 Clinical photographs of a patient with incomplete androgen insensitivity syndrome. Note the slightly enlarged clitoris and also the normal looking vagina

- A diagnosis of incomplete androgen insensitivity is suggested by elevated LH levels, with reference range levels of plasma DHT and 5-alpha-reductase activity in genital skin fibroblasts.
- Exogenously administered androgens do not cause adequate virilization; therefore, incomplete androgen insensitivity raises little question regarding the preferred sex with which to rear the child.



Figs. 31.37 and 31.38 Clinical intraoperative photographs showing clitroplasty in a patient with incomplete androgen insensitivity syndrome

- Partial androgen insensitivity syndrome results in ambiguous genitalia and there is no consensus regarding whether to raise a child with this form as male or female.
- An early gonadectomy and feminizing genitoplasty are recommended in infancy by some authors.
- In recent years the tendency has been to postpone surgery until the child has expressed a clear gender preference and is old enough to participate actively in decisions about his/her medical treatment.
- Nearly one third of patients develop a dysgerminoma or gonadoblastoma; therefore, gonadectomy becomes important as soon as the diagnosis is recognized.
- The diagnosis of incomplete androgen insensitivity syndrome is suggested by:
  - Elevated LH levels.
  - Normal levels of plasma DHT.
  - Normal 5-alpha–reductase activity in genital skin fibroblasts.
- These patients are managed with (Figs. 31.37 and 31.38):
  - Early gonadectomy
  - Clitroplasty
  - Feminizing genitoplasty
  - Hormonal replacement at puberty to induce female secondary sexual characteristics.
  - Patients who are assigned as males will require hormonal treatment to virilize their body.
- Mild androgen insensitivity syndrome is also described.
  - This is a condition which mildly affects a genetic male's ability to recognize androgens.
  - It is considered a form of androgen insensitivity syndrome and is considered the least severe form.
  - While men generally do not need any specialized medical care related to this form, mild androgen insensitivity syndrome may result in gynecomastia and hypospadias.
  - Removal of gynecomastia and repair of hypospadias can be performed.
  - Men with mild androgen insensitivity syndrome may have reduced fertility.

31.11 Deficiency of MIS (Persistent Müllerian Duct Syndrome)

- Persistent Müllerian duct syndrome (PMDS) is also called hernia uterine inguinale.
- It is a rare condition and results from either a complete failure of the testes to produce

Müllerian Inhibiting Hormone or substance (MIH, MIS) or a failure of the Müllerian duct to respond to its secretion.

- This is seen in males with normal 46XY chromosomes.
- Both Wolffian and Müllerian ducts develop.
- These patients have normal external genitalia and usually present with undescended testes or inguinal hernia (Fig. 31.39).
- Isolated MIS deficiency is a rare syndrome and usually does not present in the newborn period because the genitalia appear to be those of a male with undescended testes.
- The most common presentation is a phenotypic male with an inguinal hernia on one side and an impalpable contralateral gonad.
- At the time of herniotomy or orchidopexy, a uterus and fallopian tube is found in the hernial sac (Fig. 31.40).
- A vas deferens is presents bilaterally, usually running close to the uterus.
- To avoid damage to the vas, care must be taken at the time of Müllerian remnants excision.
- Sometimes, the vas deferens ends blindly.
- Abnormalities in the attachment of the epididymis to the testis are also reported.
- Appropriate surgical management attempts to bring the testes into the scrotum based on the rationale that testis tumors may occur later.
- The incidence of malignancy is unknown.
- A primary or staged orchidopexy is all that is required.
- Inguinal hernia should be repaired when present.
- Surgical removal of the Müllerian duct derivatives is controversial, as malignancy in retained Müllerian structures is extremely rare and the potential fertility can be compromised by a surgical attempt to remove the Müllerian derivatives.
- The surgical management includes:
  - – Orchidopexy. This may necessitates division of the uterus to lengthen the vas.
  - – A transverse testicular ectopia may be associated with this condition. In this, both testes are found on the same side.
  - – Excision of Müllerian remnants.
    - This is still controversial
    - This is not a simple procedure and care should be taken to avoid injury to the vas.

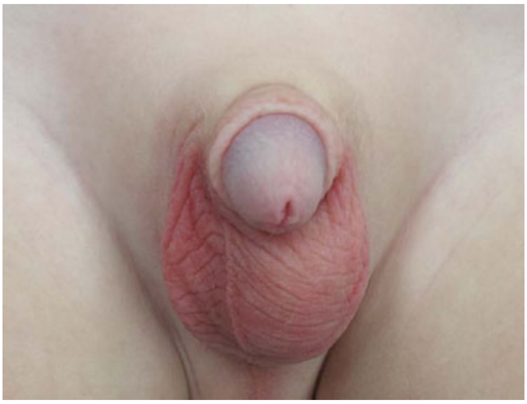


Fig. 31.39 A clinical photograph of a patient with normal looking external genitalia and undescended right testis who was found to have deficiency of MIS

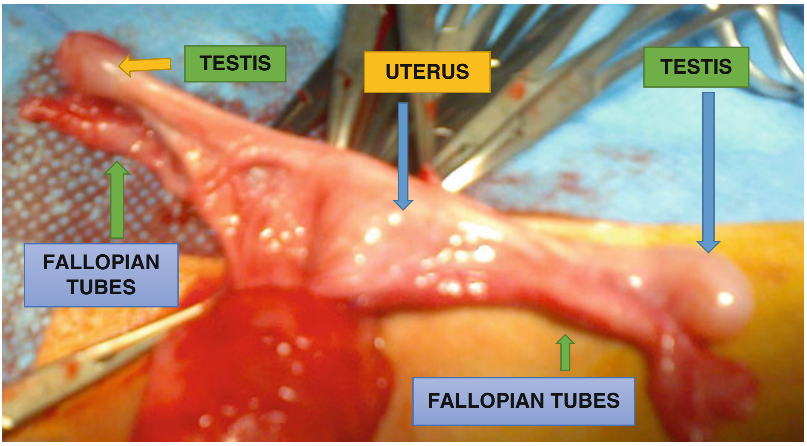


Fig. 31.40 A clinical intraoperative photograph of a patient with persistent Mulleriaan duct syndrome. Note the presence of a uterus, two fallopian tubes and two testes but no ovaries. This results from deficiency of MIS

  - Removal of Müllerian remnants is unnecessary, since the remnants rarely produce symptoms and an extremely rare risk of subsequent malignancy.

31.12 5-Alpha-Reductase Deficiency

- This is an autosomal recessive condition caused by a mutation of the 5-alpha reductase type 2 gene.
- 5-alpha reductase enzyme is important for the conversion of testosterone to dihydrotestesterone (DHT).

Deficiency of MIS (Persistent Müllerian Duct Syndrome)

- The karyotype is 46XY
- Normal male external genitalia
- Results from complete failure of the testes to produce Müllerian Inhibiting Hormone or substance (MIH, MIS) or a failure of the Müllerian duct to respond to its secretion
- Both Wolffian and Müllerian ducts develop.
- Usually present with undescended testes or inguinal hernia
- There is a uterus, two fallopian tubes and two testes with two vas deference but no ovaries
- A transverse testicular ectopia may be associated with this condition where both testes are found on the same side
- The treatment is a primary or staged orchidopexy
- Excision of Müllerian remnants is controversial

- This is seen in males with a 46XY chromosomes.
- These patients have normal testes but lacks the enzyme 5-alpha reductase in the cells of the external genitalia and urogenital sinus.
- The fetus is born with minimally virilized external genitalia (pseudovaginal perineoscrotal hypospadias).
- A 46,XY fetus with normal testes but lacking the enzyme 5-alpha reductase in the cells of the external genitalia and urogenital sinus cannot produce DHT.
- Therefore, the fetus is born with minimally virilized external genitalia (e.g., pseudovaginal perineoscrotal hypospadias), though the fetus usually has a degree of phallic enlargement, reflecting the direct action of testosterone.
- The fetus usually has a degree of phallic enlargement as a result of the direct action of testosterone.
- The striking feature in these patients is the extreme virilization at puberty. This is most likely caused by direct action of testosterone on the phallus. There will be increase in the penile size as well as the muscle mass and a masculine voice.
- The main features that do not develop are the ones depend on DHT (prostatic enlargement, facial hair, acne).
- There is a spectrum of 5-alpha-reductase deficiency which probably accounts for some of the variation in the phenotypes seen.
- These patients are fertile with the ability to have children.
- The diagnosis of 5-alpha-reductase deficiency can be confirmed as follows:
  - A patient with a 46XY karyotype.
  - A high ratio of serum testosterone to DHT.

5-Alpha-Reductase Deficiency

- An autosomal recessive condition
- Karyotype is 46XY
- Caused by a mutation of the 5-alpha reductase type 2 gene
- They have normal testes but lacks the enzyme 5-alpha reductase
- 5-alpha reductase enzyme is important for the conversion of testosterone to dihydrotestosterone (DHT)

- A high ratio of serum testosterone to DHT
- There is a spectrum of 5-alpha-reductase deficiency
- The fetus is born with minimally virilized external genitalia (pseudovaginal perineoscrotal hypospadias)
- The striking feature is the extreme virilization at puberty
- Many recommend that all patients with 5-alpha reductase deficiency should be raised as males.
- Others recommend that only the most extremely virilized infant should be raised as males.
- Many authors recommend gonadectomy and feminizing genitoplasty in these patients.

  – During the first 60 days of life, infants experience a surge of LH that obviates the need to carry out HCG stimulation, which may be useful to exaggerate the testosterone-to-DHT ratio characteristic of this syndrome.
  – The normal testosterone-to-DHT ratio is 8–16:1, while patients with 5-alpha-reductase deficiency characteristically have a ratio greater than 35:1.
  – Urinary metabolites of testosterone and DHT can be used to establish the diagnosis.
  – Cultured skin fibroblasts will demonstrate decreased 5-alpha-reductase activity.

- Gender assignment and management:
  – Gender assignment is difficult in these patients because of the major virilization that occurs at puberty.
  – Many recommend that all patients with 5-alpha reductase deficiency should be raised as males.
  – Others recommend that only the most extremely virilized infant should be raised as males.
  – The surgical results of a masculinizing operation in a mildly virilized infant are poor, and the burden to the child of growing up with inadequate genitalia hardly seems justified.
  – Many authors recommend gonadectomy and feminizing genitoplasty in these patients.

31.13 Gonadal Dysgenesis

- Gonadal dysgenesis refers to a variety of congenital developmental disorders in which the development of the indifferent embryonic gonads to differentiated gonads is inhibited.
- The gonads are usually hypoplastic and dysfunctional with a complete germ cell deficiency.
- This loss leads to extremely hypoplastic (underdeveloped) and dysfunctioning gonads mainly composed of fibrous tissue, hence the name streak gonads—i.e., a form of aplasia in which the ovary is replaced by functionless tissue.
- The accompanying hormonal failure also prevents the development of secondary sex characteristics in either sex, resulting in a sexually infantile female appearance and infertility.
- The group of gonadal dysgenesis disorders includes:
  – Pure gonadal dysgenesis (46,XX or 46,XY = Swyer syndrome)
  – Mixed gonadal dysgenesis (mosaic 45,X0/46,XY etc.)
  – Partial gonadal dysgenesis
  – Turner syndrome
  – Dysgenetic male pseudohermaphroditism (DMP)
  – XX gonadal dysgenesis
  – Perrault syndrome
- A streak gonad:
  – A gonads only consisting of fibrous tissue and with no histological evidence of germ cells.
- A dysgenetic testis:
  – A dysgenetic testis histologically demonstrates immature and hypoplastic testicular

  tubules in a stroma characteristic of ovarian tissue but that lacks oocytes.
  - This stroma has the appearance of that seen in streak gonads and may help to explain the similarities of these syndromes.
  - Dysgenetic testes have a high risk for malignancy and can develop into malignant germ cell tumors such as dysgerminomas or gonadoblastomas.
  - In contrast, dysgenetic ovaries do not seem to comprise an increased risk for malignancy, as the existence of the GBY region on the Y chromosome as well as the testes specific protein gene (TSPY) on the Y chromosome predispose for a malignant transformation
- Embryology and pathogenesis:
  - The genetic sex is determined by the karyotype, which is either XX or XY.
  - The Y chromosome contains the SRY (sex determining region of the Y chromosome), which induces male sex development during embryogenesis (The development of the testes).
  - In the absence of the SRY or in the presence of a second X chromosome, ovaries develop.
  - This then determines the gonadal sex.
  - The testes produce testosterone as well as the anti-müllerian hormone (AMH), which suppresses the development of the müllerian ducts, precursors of the fallopian tubes, the uterus and the upper vagina.
  - The ovaries produce estrogens.
  - As a response to this hormone production of the testes or ovaries, the phenotypic sex develops.
  - As a result, if a gonad cannot express its sexual identity via its hormones—as in gonadal dysgenesis—then the affected person, no matter whether their chromosomes are XY or XX, will develop external female genitalia. Internal female genitalia, primarily the uterus, may or may not be present depending on the etiology of the disorder.
  - In both sexes, the commencement and progression of puberty require functional gonads that will work in harmony with the hypothalamic and pituitary glands to produce adequate hormones.
  - For this reason, in gonadal dysgenesis the accompanying hormonal failure also prevents the development of secondary sex characteristics in either sex, resulting in a sexually infantile female appearance and infertility.
  - Dysgenetic testes do not produce a sufficient amount of testosterone in order to achieve a complete masculinization of the genitals.
  - Furthermore, AMH, which suppresses the female anlage of the genitals is not produced.
  - The clinical picture is heterogeneous.
    - Depending on the expression, the phenotype can be female or, in milder cases, the genitals can be male or only present with hypospadias.
  - Gonadal dysgenesis will occur if there is an absence of both Müllerian inhibiting factor and testosterone.
    - The absence of testosterone will result in regression of the Wolffian ducts; normal male internal reproductive tracts will not develop.
    - The absence of Müllerian inhibiting factor will allow the Müllerian ducts to differentiate into the oviducts and uterus.
    - The affected person will possess female-like internal and external reproductive characteristics, lacking secondary sex characteristics.
    - The genotype may be either 45,XO, 46,XX or 46,XY.
- The gonads are usually asymmetrical:
  - A dysgenetic testis on one side composed of disordered tubules, often sparse and abundant stroma
  - A streak gonad on the other side, composed of ovarian stroma but with no oocytes.
- The degree of virilization is variable but all patients have a vagina and a uterus, and most have a fallopian tube, at least on the side of the streak gonad.
- Fertility has not been reported in patients with MGD.

- The sex assignment varies, and factors to consider include:
  - Prenatal androgen exposure
  - Testicular function at and after puberty
  - Phallic development
  - Gonadal location
- Risk of malignancy:
  - There is a risk of gonadal malignancy in these patients especially when a Y chromosome is present in the karyotype.
  - These malignant tumors include:
    - Gonadoblastomas
    - Seminomas
    - Embryonal cell carcinomas
- Turner syndrome:
  - The classical Turner syndrome is characterized by a short stature, missing secondary sex characteristics and webbed neck (lymphedema of the head and neck, Lymphangiosis colli).
  - It was first described by Otto Ullrich in 1930, a pediatrician from Munich.
  - In 1938, the American physician Henry Turner described this syndrome which was named after him.
  - It is also known as Ullrich-Turner syndrome
  - The development of a normal female phenotype requires the presence of two functioning X chromosomes. The loss of the second sex chromosome (X or Y) takes place postzygotically and depending on what cell stage the sex chromosome is lost, different chromosomal cell lines can be found concurrently which leads to the development of mosaicisms.
  - Turner syndrome is the most frequent form of gonadal dysgenesis.
  - The incidence is estimated to be between 1 in 3,000 and 1 in 2,500 live-born female infants.
  - In Turner syndrome:
    - 50 % of the patients have pure 45,X0 monosomy.
    - 5–10 % have a duplication of the long arm of one of the X chromosomes (46Xi(Xq)).
    - The rest are mosaicisms of 45,X0 with one or more cell lines.
  - Due to the numerous chromosomal aberrations that can cause the Turner syndrome, the clinical picture varies widely.
  - Turner syndrome is characterized by:
    - Streak gonads
    - Malformations of the internal organs
    - Hypertrophy of the clitoris
    - Hypospadias
    - The phenotype can be pure female or male.
    - In some patients, the function of the gonads is partly or completely maintained.
      - These patients can develop spontaneous onset of puberty, menstruation or even pregnancy.
      - Patients with a normal phenotype or a spontaneous onset of puberty are often carriers of mosaicisms.
      - As patients with mosaicims usually do not have any stigmata, the diagnosis can be delayed and discovered accidently during investigation of infertility or recurrent abortions.
- Partial gonadal dysgenesis:
  - Partial gonadal dysgenesis can be classified as:
    - 46XY DSD
    - Sex chromosome DSD if there is mosaicism (45X/46XY)
  - Partial gonadal dysgenesis represents a spectrum of DSD in which the gonads are abnormally developed.
  - Typically, at least one gonad is either dysgenetic or a streak.
  - The internal ducts vary according to the associated gonads
  - Although the degree of virilization varies, all patients have a vagina and a uterus, and most have a fallopian tube, at least on the side of the streak.
  - Estrogen support is required if these patients are raised as females.
  - If the uterus remains in place, unopposed estrogen can increase incidence of endometrial carcinoma; thus, these patients must be cycled with a combination of estrogen and a progestational agent.

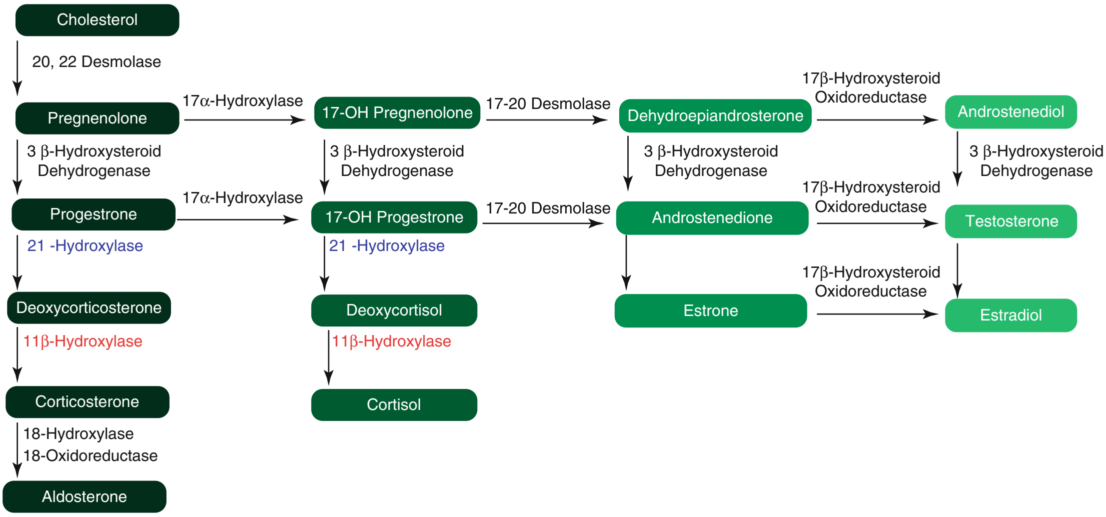
- Mixed gonadal dysgenesis (MGD):
  - – Mixed gonadal dysgenesis (MGD) is the second most common cause of ambiguous genitalia in a newborn.
  - – It is characterized by unusual and asymmetrical gonadal development.
    - A streak gonad is usually present on one side and a testis (usually dysgenetic) on the opposite side.
  - – A number of chromosomal karyotypes have been reported but most patients with MGD have a mosaic karyotype, 45XO/46XY or 46,XX/46,XY.
  - – It is assumed that the 45,X0 cell line causes the development of the streak gonads and the 46,XY cell line is associated with the differentiated testis.
  - – In MGD, 25% of gonads, including streak gonads, can be expected to undergo malignant change, most commonly to gonadoblastoma.
  - – In addition to gonadoblastomas, seminomas and embryonal cell carcinomas may develop.
  - – Gender assignment for patients with MGD remains controversial.
  - – The clinical picture of mixed gonadal dysgenesis is heterogeneous.
    - The external genitals can have a phenotype ranging from female to male.
    - In most cases, the genitals are intersexual with a hypertrophy of the clitoris or hypospadias.
    - As the AMH secretion is also affected to different degrees, variable constellations of the müllerian duct derivatives are possible.
    - In most cases, the gonads have developed asymmetrically (a streak gonads on one side and normal or dysgenetic testes on the other side). The testis is usually intra-abdominal or inguinal.
    - In some cases, the streak gonads are bilateral.
    - The testes have a normal histological appearance before puberty. Sertoli and Leydig cells are present but germ cells are missing.
  - – As in all gonadal dysgeneses with Y-chromosomes, there is a certain risk for malignancy, which is why gonadectomy is indicated as early as possible.
- Dysgenetic male pseudohermaphroditism (DMP):
  - – This term is used to describe patients with bilaterally dysgenetic testes and incomplete virilization of the internal sex ducts and external genitalia.
- XX gonadal dysgenesis:
  - – This is a type of female hypogonadism in which no functional ovaries are present to induce puberty in an otherwise normal girl whose karyotype is found to be 46,XX.
  - – The presence of nonfunctional streak ovaries is associated with low estrogen levels (hypoestrogenic) and high levels of FSH and LH.
  - – Estrogen and progesterone therapy is the recommended treatment.
- Perrault syndrome:
  - – In 1951, Perrault reported the association of gonadal dysgenesis and sensorineural hearing loss.
- Management:
  - – Early gonadectomy is recommended in these patients.
  - – The gender assignment for patients with DMP and MGD remains controversial.
  - – There are those who recommend a male gender assignment for those patients who are sufficiently virilized.
  - – Others recommend a female gender assignment for patients with MGD because a uterus and vagina are present always and half of these patients have inadequate external virilization.
  - – Patients who are raised as females require estrogen supplements.
  - – If the uterus remains in place, the unopposed estrogen can increase the incidence of endometrial carcinoma and these patients should receive a combination of estrogen and a progestational agents.
- Pure gonadal dysgenesis:
  - – Pure gonadal dysgenesis is defined as the absence of differentiated gonads, but with

normally developed internal and external genitalia.

- The karyotype is either 46,XX or 46,XY.
  - The 46XX type is usually transmitted by autosomal recessive inheritance, while the 46,XY type is transmitted by X-linked inheritance.
  - The 46,XY type is named after G. J. Swyer, the first person who described the syndrome (Swyer syndrome).
  - A major part of the patients carries a mutation of the SRY gene which inhibits the differentiation of the testes.
  - Due to the lack of testosterone and AMH, the vagina and the uterus develop.
- These patients are phenotypically females.
- They have bilateral streak gonads appearing as ovarian stroma without oocytes.
- Hypogonadism with elevated gonadotropin levels is a characteristic finding in the affected patients.
- These patients are usually not recognized in the newborn period and they present at puberty when they do not undergo normal pubertal changes.
- The secondary sex characteristics fail to develop, and or the menarche is absent (primary amenorrhea)
- Girls with Turner syndrome (45XO) may be detected earlier by noting the characteristic associated anomalies of short stature, webbing of the neck, and wide-spaced nipples.
- Swyer Syndrome (Also known as Pure Gonadal Dysgenesis or XY gonadal dysgenesis):
  - This is a type of hypogonadism in a person whose karyotype is 46,XY.
  - The person is phenotypically female with streak gonads, and if left untreated, will not experience puberty.
  - Such gonads are typically surgically removed as they have a significant risk of developing tumors.
  - These patients are treated with female hormone replacement therapy.
- Neither Turner syndrome (45XO) nor the 46XX type of pure gonadal dysgenesis appears to be associated with increased risk of gonadal malignancy.
- Histologically, there are streak gonads composed of fibrous tissue or dysgenetic testes with Leydig and Sertoli cells but no or only few germ cells, which have a malignancy potential of 25 %.
- Patients with 46XY pure gonadal dysgenesis on the other hand carry a significant risk for malignancy. Nearly one third of patients develop a dysgerminoma or gonadoblastoma; therefore, gonadectomy should be done as soon as the diagnosis is confirmed.
- In 46,XX gonadal dysgenesis, the patient usually has a homozygote or heterozygote mutation of the FSH receptor gene.
- An FSH receptor mutation causes a female phenotype in the absence of secondary sex characteristics.
- The leading symptom is usually primary amenorrhea that results from a primary or premature ovarian insufficiency.
- A homozygote FSH receptor mutation in patients with a female karyotype always causes ovarian insufficiency and infertility, while the heterozygote or the homozygote form in patients with a male karoytype not always causes gonadal dysfunction or infertility.
- Treatment of those with pure gonadal dysgenesis is primarily limited to appropriate estrogen and progesterone replacement therapy.
- This is important for the maintenance of bone density and for the induction of female genital development.
- Pure gonadal dysgenesis syndromes can be familial and call for genetic counseling.
  - Turner syndrome appears sporadically, suggesting a postzygotic error.
  - The 46XX type of pure gonadal ysgenesis is transmitted as autosomal recessive.
  - The 46XY type is inherited as an X-linked recessive trait

31.14 Deficient Testosterone Biosynthesis

- Testosterone is produced from cholesterol.
- Production of testosterone from cholesterol involves five enzymatic steps, and defects have been identified at each step.
- Of these five enzymes, three are shared with the adrenal glands, and their deficiency leads to ambiguous genitalia and symptoms of CAH. These three enzymes are:
  - 20-alpha hydroxylase
  - 3-beta-hydroxysteroid dehydrogenase
  - 17-alpha hydroxylase
- The other two enzymes occur only as part of the normal testosterone biosynthesis and their defects leads to ambiguous genitalia without the symptoms of congenital adrenal hyperplasia.
- These two enzymes are:
  - 17, 20 desmolase.
  - 17-ketosteroid reductase.
- The diagnosis of these enzyme deficiencies is possible by measuring the levels of precursor products. This however is available in specialized centers only.
- During the newborn period, these patients present as 46XY gonadal males with poor virilization and ambiguous genitalia.
- The genitalia in these patients respond to exogenously testosterone.
- This help differentiating them from 5-alpha reductase deficiency which do not respond to testosterone but will respond to dihydrotestosterone.
- It is also important to treat those with CAH manifestations with steroid and mineralocorticoid replacement.
- Genetic counseling is also important in these patients as 17-alpha hydroxylase and 3-beta-hydroxysteroid dehydrogenase deficiencies are transmitted as autosomal recessive traits.
- Other rare causes of testosterone production deficiencies include:
  - Leydig cell agenesis
  - Leydig cell hypoplasia
  - Abnormal Leydig cell gonadotropin receptors
  - Delayed receptor maturation


Cholesterol
20, 22 Desmolase
Pregnenolone
17α-Hydroxylase
17-OH Pregnenolone
17-20 Desmolase
Dehydroepiandrosterone
17β-Hydroxysteroid Oxidoreductase
Androstenediol
3 β-Hydroxysteroid Dehydrogenase
3 β-Hydroxysteroid Dehydrogenase
3 β-Hydroxysteroid Dehydrogenase
3 β-Hydroxysteroid Dehydrogenase
Progestrone
17α-Hydroxylase
17-OH Progestrone
17-20 Desmolase
Androstenedione
17β-Hydroxysteroid Oxidoreductase
Testosterone
21 -Hydroxylase
21 -Hydroxylase
Deoxycorticosterone
Deoxycortisol
Estrone
17β-Hydroxysteroid Oxidoreductase
Estradiol
11β-Hydroxylase
11β-Hydroxylase
Corticosterone
Cortisol
18-Hydroxylase
18-Oxidoreductase
Aldosterone

31.15 Ovotestis Disorders of Sexual Development

- This refers to a rare condition in which the histology of a gonad contains both ovarian and testicular tissues (Figs. 31.41 and 31.42).
- A diagnosis of Ovotestis-DSD is based solely on the presence of ovarian and testicular tissue in the gonad and not on the characteristics of the internal and external genitalia.
- This was formerly known as true hermaphroditism.
- They account for less than 10 % of DSD cases.
- The appearance of the genitalia varies widely in this condition.
- Although ambiguity is the rule, the tendency is toward masculinization.
- Presentation:
  - In the neonatal period, these patients usually presents with ambiguous genitalia.
  - Although some cases of ovotestis DSD are diagnosed in the newborn period, only 20 % are diagnosed prior to age 5 years.
  - Most cases of ovotestis DSD are diagnosed in the pubertal period when the young male begins to experience feminization.
  - Inguinal hernia and cryptorchidism are common in these patients.
- The peripheral karyotype is also variable in these patients and include:
  - 46,XX ovotesticular DSD. This is the most common karyotype, seen in 60–80 % of patients.
  - 46, XY ovotesticular DSD. This karyotype is found in about 10–15 % of patients.
  - 46,XX/46,XY peripheral karyotype
- A translocation of the gene coding for HY antigen from a Y chromosome to either an X chromosome or an autosome presumably explains the testicular material in a patient with a 46,XX karyotype.

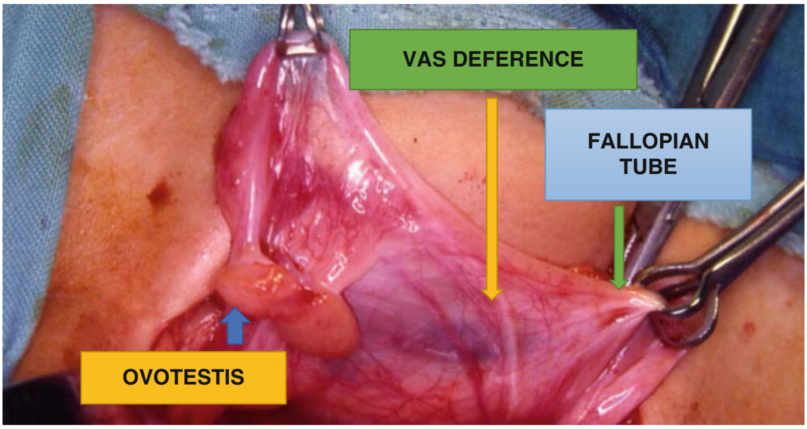


Fig. 31.41 A clinical intraoperative photograph of a patient with ovotesticular DSD. Note the ovotestis, the vas deference and Fallopian tube

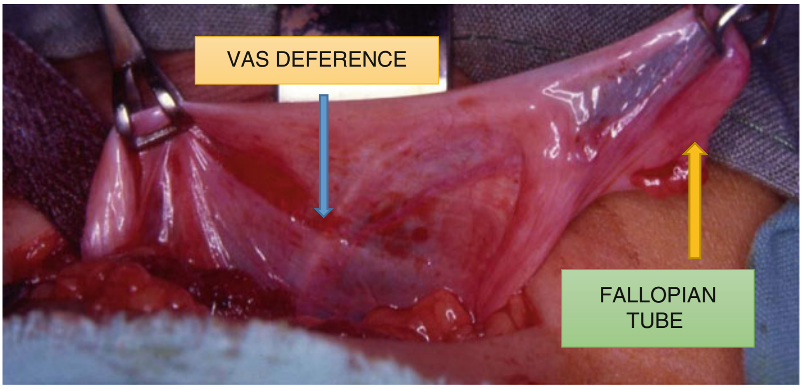


Fig. 31.42 A clinical intraoperative photograph of a patient with ovotesticular DSD. Note the presence of a fallopian tube and a vas

- More problematic is how a patient with a 46,XY karyotype can have ovarian tissue, given that two X chromosomes are believed to be necessary to normal ovarian development. Possibly, unidentified XX cell lines are present in these patients.
- The gonads in these patients may be:
  - Ovotestis on both sides
  - A combination of an ovary on one side and a testis or ovotestis on the other side.
  - Ovotestes on both sides are the most frequent gonad present (60 %), followed by the ovary and then the testis (9 %).
  - When an ovotestis is present, one third of the patients exhibit bilateral ovotestes.
  - A testicle, when present, is more likely to exist on the right (57.4 %), and an ovary, when present, is more commonly seen on the left (62 %).
  - A palpable gonad is present in 61 % of patients; of these, 60 % are found to be an ovotestis.
  - In 80 % of patients with ovotestes, testicular and ovarian tissues are aligned in an end-to-end fashion, emphasizing the need for a long longitudinal biopsy.
  - In 20 % of patients with ovotestes, testicular tissue is found in the hilar region of the gonad, reemphasizing the need for an adequate and deep biopsy.
  - An ovary, when found, is situated most commonly in the normal anatomic intra-abdominal position, and extremely rare an ovary can be found in the hemiscrotum.
  - The least common gonad in ovotesticular DSD is the testis; when present, a testis is found approximately two thirds of the time in the scrotum, emphasizing that normal testicular tissue is most likely to descend fully.
  - Ovotestes may present with either a fallopian tube or a vas deferens but usually not with both.
  - If a fallopian tube has a fimbriated end, the end is closed in most patients, perhaps contributing to the usual lack of fertility.
  - Although fertility is rare in this setting, it has been reported.
  - Gonadal tumors also are rare but have been reported.
- The anatomical location of these gonads is variable:
  - The ovotestis tends to be anatomically located in:
    - A normal ovarian position
    - In the labioscrotal fold
    - In the inguinal canal
    - At the internal inguinal ring
  - Ovaries, when found, can occupy the normal abdominal position, although they may occasionally be found at the internal inguinal ring.
    - Interestingly, ovaries occur more commonly on the left side than the right.
    - The testes are usually found in the scrotum, although they can be found at any level along the path of embryonic descent from abdomen to scrotum, frequently presenting as inguinal hernias.
  - Many patients with ovotesticular disorder of sexual development have a uterus.
  - Internal duct development usually corresponds to the adjacent gonad so that:
    - Müllerian duct structures are usually seen on the gonad side(s) not containing testicular tissue.
    - Wolffian duct structures are usually seen on the gonad side(s) containing functioning testicular tissue.
- Ovotestes are usually made up of ovarian part and testicular part with connective tissue between then. This is important surgically when separating the ovarian components from the testicular components. However, on rare occasions, it is difficult to separate the two.
- Most patients with ovotestes DSD are reared as males due to the size of the phallus but male reproductive potential in these individuals is rare.
- This is not the case in those who are assigned a female gender with 46,XX chromosomes who have fertility potential.
- They also have varying degrees of labioscrotal fusion and/or hypospadias which needs correction.
- Most cases of ovotesticular DSDs are diagnosed during the adolescent period and because of functioning normal ovarian tissue, most of them experience breast development

at puberty, and approximately two-thirds of those with a 46,XX peripheral karyotype menstruate.

- Patients with ovotestes DSD are at risk of gonadal tumors which occur in 2.6 % of the cases.
  - The testis or testicular part of an ovotestis is likely to be dysgenetic with a risk of developing dysgerminomas, seminomas, gonadoblastomas, and yolk sac carcinomas.
  - The risk is more in those with 46,XY karyotype.
  - Benign tumors, including mucinous cystadenomas, benign teratomas, and Brenner tumors, have also been reported in these patients.
- Investigations:
  - Chromosomal analysis
  - Hormonal evaluation
    - Serum 17-hydroxyprogesterone:
      - Patients with ovotesticular DSD have normal levels of this hormone which differentiate them from those with congenital adrenal hyperplasia.
    - Basal and stimulated serum androgens:
      - The presence of functional testicular tissue can be determined with the use of a human chorionic gonadotropin (HCG) stimulation test.
      - In this test, basal levels of testosterone, dehydroepiandrosterone sulfate, androstenedione, and dihydrotestosterone (DHT) are measured.
      - HCG (3,000–5,000 IU/m^2/d IM) is then administered for 5 days.
      - On the day 6, the serum hormone levels tests are repeated.
      - A rise in serum testosterone demonstrates the presence of functioning Leydig cells.
      - Elevated testosterone precursors may suggest a specific defect of testosterone synthesis.
      - Failure of testosterone to reduce to DHT may suggest a 5-alpha reductase deficiency.
    - Basal and stimulated estrogen levels:
      - The presence of functional ovarian tissue can be determined with the use of gonadotropin or clomiphene citrate administration.
      - An estradiol response to gonadotropin stimulation is a reliable test to differentiate ovotesticular disorder of sexual development from other disorders.
  - Radiological evaluation:
    - A scrotal ultrasonography is used to detect occult gonads.
    - A genitogram is used to evaluate the structure of the urethra and to confirm the presence of a vagina and uterus (Fig. 31.43).
    - An intravenous pyelogram is important to rule out any associated urinary tract anomalies.
    - Abdominal and pelvic ultrasonography, CT scan, or MRI are useful in delineating the gonads and duct structures.
- Management:
  - The main point in the management of these patient is gender assignment.
  - This must take in consideration two main points:
    - The potential for normal sexual function
    - The potential for future reproductive function
  - It is important to establish histological confirmation with a gonadal biopsy which can be done via a laparotomy or Laparoscopically.
  - Surgery in these patients should be planned with the previous two goals in mind and conservative gonadal surgery is the procedure of choice.
  - Ovotestes frequently can be separated into ovarian and testicular components and partial resection of ovotestes is feasible in a

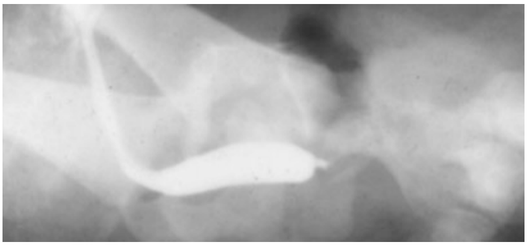


Fig. 31.43 A genitogram showing a normal looking vagina in a patient with ovotesticular DSD

large number of these patients which should be guided by intraoperative histologic confirmation (Fig. 31.44).
- It allows preservation of gonadal tissue concordant with sex of rearing, and removal of all discordant tissue.
- The ovarian tissue can be preserved in people who are given a female sex assignment. Frequently, these patients demonstrate normal ovarian function and potential for reproduction.
- The aim is to preserve the gonadal tissue that is concordant with sex of rearing, and excision of all other tissue.
- Cystoscopy may be used to determine the position of entry of the vagina into the urethra or urogenital sinus.
- Prophylactic gonadectomy should be considered in those who manifest signs of virilization or are at an increased risk of gonadal malignancy.
- Hormone replacement might be required for those with pubertal delay.
- The following operative procedures are indicated in patients with ovotestes DSD depending on the sex of rearing:
  - Excision of intra-abdominal testis or streak gonads in those with Y chromosome-DNA because of increased risk of malignant transformation.
  - Excision of wolffian structures and testicular tissue if the patient has been given a female gender assignment.
  - Excision of Müllerian structures and ovarian tissue if the patient has been given a male gender assignment.
  - Orchiopexy to treat an undescended testis in a patient with male gender assignment.
  - Clitoral recession, vaginoplasty, and labioscrotal reduction are necessary for people with ovotesticular DSD who are given a female sex assignment.
  - These feminizing procedures should be performed as early as possible as a 1-stage procedure.
  - Correction of penile deviation and hypospadias should be done in those given a male gender assignment.

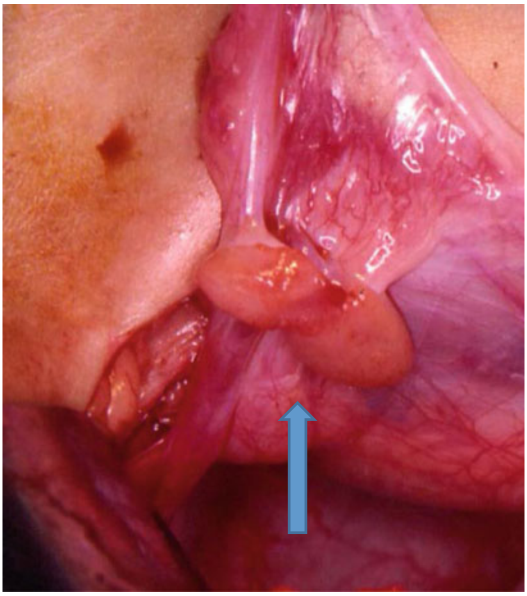


Fig. 31.44 A clinical intraoperative photograph of a patient with ovotesticular DSD. Note the presence of an ovotestis on this side

31.16 Other Rare Disorders of Sexual Development

17β-Hydroxysteroid dehydrogenase deficiency:

- This condition is characterized by impaired androgen and estrogen synthesis in both males and females.
- The end result is:
  - Pseudohermaphroditism/undervirilization in males.
  - Excessive virilization of females.

Aromatase deficiency:

- Aromatase is the enzyme that catalyzes conversion of androgens into estrogens.
- As a result of this enzyme deficiency, there will be androgen excess and estrogen deficiency.
- This results in inappropriate virilization of females.
- They have normal female external genitalia.
- They may have cliteromegaly.
- These female patients can present:

  - During childhood and adolescence with cystic ovaries
  - At puberty with:
    - Primary amenorrhea
    - Failure of breast development
    - Virilization
    - Hypergonadotrophic hypogonadism

Aromatase excess syndrome:
- This is also called familial hyperestrogenism.
- In this condition, there is excessive estrogen production.
- It is seen in males and females.
- In males, it will result in feminization without pseudohermaphroditism.
  - A normal male external genitalia at birth.
  - Female secondary sexual characteristics at puberty.
- In females, it will lead to hyperfeminization.

Klinefelter syndrome:
- This condition is seen in males born with at least one extra female chromosome.
- It is also called XXY syndrome.
- The chromosomal karyotype is 47, XXY.
- Though the most common chromosomal variation is 47, XXY, other variations may also be 48, XXXY or 49, XXXXY.
- It is a common occurrence, affecting 1 in 500 to 1,000 men.
- While some men may have no issues related to the syndrome, others may experience:
  - Gynecomastia
  - Micropenis
  - Cognitive difficulties
  - Hypogonadism
  - Reduced fertility/infertility
  - Little or no facial hair.
- Testosterone therapy may be pursued by men who desire a more masculine appearance and those with gynecomastia may opt to undergo a reduction mammoplasty.
- Men who wish to father children may be able to do so with the help of IVF.

Triple X syndrome:
- A condition that occurs in a female born with an extra female chromosome.
- The chromosomal karyotype is 47, XXX.
- It is a common condition affecting 1 in 1,000 females.
- It is a benign condition and generally does not cause health issues or abnormal development.

Aphallia:
- This is a rare congenital condition where a male is born without a penis or where a female is born without a clitoris.
- It should not be confused with intentional or accidental amputation of the genitalia.

Aposthia:
- A congenital defect where a male is born without a foreskin.

Diphallia:
- This is also known as penile duplication, diphallic terata, and diphallasparatus.
- This is extremely rare.
- It is characterized by a male born with two penises.
- The penises may be side by side or one on top of the other.
- The penises may be of equal size or with one penis being distinctively larger than the other.
- Both penises may be suitable for urination and intercourse.
- Men with diphallia may be sterile.

Micropenis:
- This is also known as microphallus.
- It is defined as a penis that measures 3 in. (7.62 cm) or less in length when erect.
- It is a common condition, occurring in 1 in 200 men.
- Micropenis may be the result of undervirilization during fetal development or may be caused by an underlying intersex condition, such as mild androgen insensitivity syndrome, partial androgen insensitivity syndrome, or Klinefelter syndrome.
- It may also be considered a natural variation of penis size.

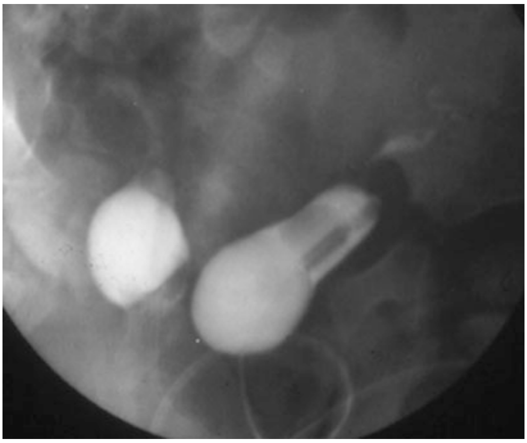


Fig. 31.45 A genitogram showing a double vagina

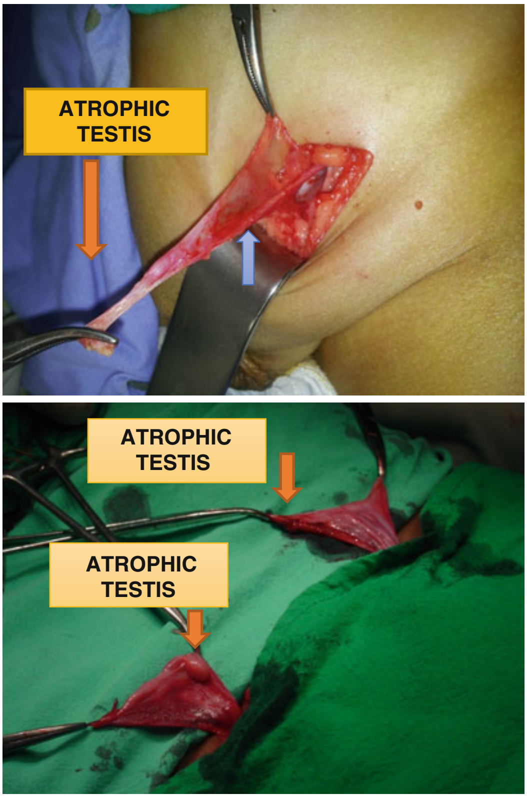
- While the majority of men have no issues with having a micropenis, some may opt to use a prosthetic penis or undergo penile enlargement to increase the size of their penis.

Uterus didelphys:

- This is also known as double uterus.
- It is seen in a female born with two uteri.
- It is often accompanied by two vaginas (Fig. 31.45).
- This is a benign condition and females with uterus didelphys usually have normal sex lives and pregnancies.

Bilateral vanishing testes:

- 'Bilateral vanishing testes' implies absent gonads that could be due to mutation, exposure to a teratogen, or bilateral torsion (Figs. 31.46 and 31.47).
- The karyotype is typically 46,XY.
- The phenotype shows a male with undescended testes.
- Laparoscopy can detect rudimentary cord structures with no recognizable testicular tissue histologically.
- These patients will require androgen replacement and testicular prostheses.
- Embryonic testicular regression syndrome is a variant of bilateral vanishing testes in which the testicular function is lost early in embryonic life. This results in individuals with ambiguous genitalia.



Figs. 31.46 and 31.47 Clinical intraoperative photographs showing unilateral and bilateral atrophic testes. These are usually secondary to intrauterine torsion of testes. Note the presence of a vas

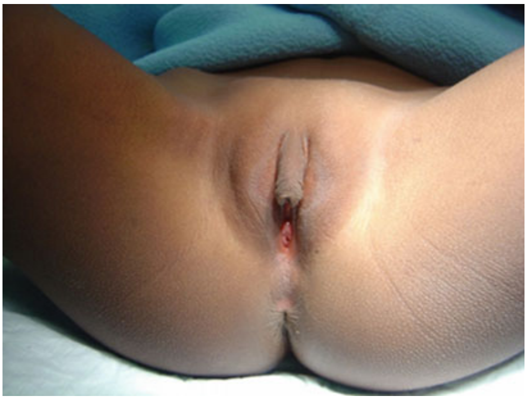


Fig. 31.48 A clinical photograph showing cliteromegaly. Note the normal external genitalia

Clitoromegaly:

- A clitoris that is considered larger than average (Fig. 31.48).

- While clitoromegaly may be a symptom of an intersex condition, it may also be considered a normal variation in clitoris size.
- Clitoromegaly causes no health issues.
- Surgical reduction of the clitoris or its complete removal may be performed to normalize the appearance of the genitalia.
- While female genital mutilation is outlawed in many countries, reduction or the removal of the clitoris in cases of clitoromegaly are generally exempt, despite the fact that it is a non-therapeutic and sexually damaging surgery.
- Clitoromegaly may also be caused by females using testosterone or anabolic steroids for purposes related to female to male gender transition or bodybuilding.

Combined 17α-hydroxylase/17,20-lyase deficiency:

- A condition which presents as a combination of the symptoms of congenital adrenal hyperplasia and isolated 17, 20-lyase deficiency.

Estrogen insensitivity syndrome (EIS):

- This is the estrogen counterpart to androgen insensitivity syndrome.
- It is extremely rare, with only one verified case having been reported.
- A biological male presented with tall stature, a heightened risk of osteoporosis, and sterility.

Isolated 17,20-lyase deficiency:

- A condition that is characterized by an either partial or complete inability to produce androgens and estrogens.
- It results in partial or complete feminization and undervirilization in males and in a delayed, reduced, or absent puberty in both sexes, in turn causing sexual infantilism and infertility, among other symptoms.

Leydig cell hypoplasia:

- A condition solely affecting biological males
- It is characterized by a partial or complete inactivation of the luteinizing hormone receptor, resulting in stymied androgen production.
- Patients may present at birth with a fully female phenotype, ambiguous genitalia, or only mild genital defects such as micropenis and hypospadias.
- Upon puberty, sexual development is either impaired or fully absent.

Pseudovaginal perineoscrotal hypospadias (also known as PPSH):

- This is a form of ambiguous genitalia which is characterized by:
  - A phallic structure that is smaller than a penis but larger than a clitoris
  - A chordee
  - Hypospadias
  - A shallow vagina

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A.H. Al-Salem, *An Illustrated Guide to Pediatric Urology*, DOI 10.1007/978-3-319-44182-5

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